Chapter 4
Respiratory Diseases

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Introduction

Smoking has adverse health effects on the entire lung—affecting every aspect of lung structure and function—including impairing lung defenses against infection and causing the sustained lung injury that leads to chronic obstructive pulmonary disease (COPD). In fact, among the postulated causes of COPD are acute respiratory infections, for which smokers are at an increased risk. This chapter addresses smoking and acute and chronic respiratory diseases other than lung cancer (see Chapter 2, "Cancer"), and discusses the relevant evidence of the underlying mechanisms. COPD was the focus of the 1984 Surgeon General's report (U.S. Department of Health and Human Services [USDHHS], 1984), and a number of previous reports have addressed acute respiratory infections, which can range in severity from minor to fatal. This chapter emphasizes acute respiratory illnesses and COPD, which are leading causes of *morbidity* and mortality in the United States and worldwide.

Acute Respiratory Illnesses

Acute respiratory illnesses are presumed to have an infection as the predominant underlying cause. Smoking might act *to increase the frequency* or severity of infections. In this section, acute respiratory infections are examined separately for persons with and without preexisting chronic obstructive lung disease. Because most patients with smoking-related chronic bronchitis frequent exacerbations of their underlying disease. Whenever possible, effects of smoking on the incidence of disease are distinguished from effects on the severity of the disease.

A MEDLINE search was conducted to identify relevant studies published between *1966 and 2000*. To identify studies focusing on the biologic basis of and the evidence linking smoking and acute respiratory infections in persons without COPD, the following Medical Subject Headings (MeSH) terms were searched: "respiratory tract infections" and "smoking," "respiratory tract infections" and "immunology," "smoking" and "immunology," "nicotine" and "immunology," and "smoking" and "respiratory tract infections" and "epidemiology." To identify studies *focusing on smoking and acute respiratory infections* accompanied by COPD and asthma, the MeSH term "lung diseases, obstructive" was searched in combination with multiple key words: "antibiotic(s)," "respiratory infection(s)," "respiratory tract infection(s)," "infection(s)," "Tecumseh," "immunization," and "immunotherapy." The MeSH terms "bronchitis" and "asthma" were also searched in conjunction with the above key words. The searches were then repeated substituting the key words "COPD," "chronic obstructive pulmonary disease," "asthma," "chronic bronchitis," and "acute bronchitis." The Cochrane database was also searched. All searches included a hand search of bibliographies and authors' files.

Acute respiratory illnesses are usually divided into those that include the upper respiratory tract (nose and pharynx) and larynx, and those that include the lower respiratory tract (below the larynx). In people with normal immune systems, viruses account for many cases of upper respiratory syndromes (Gwaltney 1995c); acute bronchitis (Gwaltney 1995a), bronchiolitis (Hall and Hall 1985), and a *majority* of pneumonia cases (Marrie et al. 1989). Bacteria can cause pharyngitis (Gwaltney 1995b) and some pneumonias (Marrie et al. 1989). Cigarette smoke combustion products reportedly increase morbidity and mortality in acute respiratory infections by impairing physical defenses in the respiratory tract, and by impairing cellular and humoral immune responses to microbes (Donowitz and Mandell 1995). Moreover, the effects of smoking can be expected to differ in respiratory infections caused by viruses and in infections caused by bacteria, because each class of microbes stimulates different immune responses specific to the infection (Mandell et al. 1995).

Conclusions of Previous Surgeon General's Reports

Previous Surgeon General's reports on smoking and health have noted possible adverse effects of *cigarette smoking on acute respiratory infections. The 1979* report (U.S. Department of Health, Education, and Welfare [USDHEW] 1979) cited data from the 1964–1965 Health Interview Survey, which found a higher age-adjusted incidence of self-reported influenza in male and female smokers when compared with nonsmokers, and more upper respiratory illnesses (URIs) in female smokers than in female nonsmokers. The 1989 report (USDHHS 1989a) identified a number of studies that reported higher mortality ratios for smokers *than for nonsmokers suffering from respiratory* tuberculosis (the range of ratios was 1.27–5.0 in three studies), and from influenza and pneumonia as one combined category (the range of ratios was 1.4–2.6 in seven studies). The 1990 report focused on the health benefits of smoking cessation, and it comprehensively reviewed evidence suggesting that smoking increased the risk of acute respiratory illnesses (USDHHS 1990).

Providing a more detailed analysis of the smoking-related mortality data presented in the 1989 report, *the 1990 report identified* exposure response relationships between mortality from pneumonia and influenza and the number of cigarettes currently smoked, and identified reductions in mortality rates of former smokers in relation to years of not smoking (USDHHS 1990). A review of possible mechanisms related to acute respiratory illnesses documented a variety of effects on host defenses: increases in peripheral blood total leukocyte counts, increases in polymorphonuclear leukocyte and monocyte counts, *decreases in monocyte intracellular killing*, decreases in the CD4/CD8 ratio in heavy smokers, decreases in concentrations of serum immunoglobulins (other than IgE), an increase in alveolar macrophage release of superoxide anions, a decrease in microbicidal activity of the macrophages, and a blunted immune response to an influenza vaccination. Although the 1990 report noted that smoking cessation restored many of these impaired defenses, it also found that few epidemiologic studies directly addressed the effects of smoking on acute respiratory morbidity. Conflicting data were observed for nonspecific acute lower respiratory illnesses (LRIs), but findings for increased morbidity from influenza virus infections in smokers were more consistent. The 1994 report (USDHHS 1994), which focused on young people, added little new information.

Biologic Basis

Animal Studies

More than 25 years ago, in vitro exposure of rabbit alveolar macrophages to a water soluble fraction of tobacco smoke was shown to impair the ability of macrophages to kill bacteria (Green and Carolin 1967). An extensive body of data has since accumulated on the effects of exposure to tobacco smoke on immune and cellular function in animal models. However, differences in responses among species to different experimental exposures of tobacco *smoke and* its products make it difficult to provide a simple, unifying summary of the animal data. Impaired immunoglobulin responses to immunization (Roszman and Rogers 1986) dose-dependent decreases in responses to T cell and B cell mitogens have been reported for both short-term in vitro (Roszman et al. 1975) and in vivo (Johnson et al. 1990) exposures to tobacco smoke. Holt and colleagues (1990) provide a comprehensive review of in vivo subchronic exposure in animals (Table 4.1) and of the *voluminous* relevant animal toxicology literature through 1990. In addition to the general immunologic effects summarized in Table 4.1, direct effects of tobacco smoke exposure on lung defenses include suppressed functioning of bronchial-associated lymphoid tissue, increased numbers of alveolar macrophages that have a higher than normal incidence of impaired generation of reactive oxygen intermediates during phagocytosis, but without clinical bacterial *capacity* (for alveolar macrophage dysfunction in Johnson et al. 1990).

Studies of the effects of nicotine on the immune function of rodents provide some insights into the effects of tobacco smoke on host defenses. Exposing rats to a four-week continuous infusion of nicotine inhibited the increase of intracellular calcium that usually happens when the T cell antigen receptor is blocked (Sopori et al. 1998). The calcium ion plays a role in the early receptor-mediated activation of cells in general (Sopori and Kozak 1998), and this effect of nicotine on calcium fluxes could explain a number of observed nicotine effects on host defenses: (1) *suppressed febrile response to turpentine-induced* abscesses in mice (Sopori and Kozak 1998), (2) decreased inflammatory response to influenza infection with an increased proliferation of virus in mice (Sopori and Kozak 1998), (3) decreased responses to T cell mitogens in mice (McAllister-Sistilli et al. 1998) (T cell anergy (Sopori and Kozak 1998)), and (4) decreased

Table 4.1 Summary of subchronic exposure to cigarette smoke on immune function in animals*

Animal species	Findings
Mice	• Increased followed by decreased mitogenic response of spleen cells • Decreased hemagglutinating and hemolytic antibody titers • Decreased primary and secondary antibody responses in cells from lungs, spleen, and lymph nodes (this finding was not uniform across studies) • Decreased lymphocyte adherence and cytotoxicity • Enhanced primary and secondary antibody responses
Monkeys	• Decreased lymphocyte response to concanavalin A (a T cell mitogen) • No effect on phytohemagglutinin and lipopolysaccharide (a B cell mitogen) responses • Decreased natural killer cell cytotoxicity

*Exposures ranged from 15–416 weeks (adapted from Table 2 in Johnson et al. 1990).

induction of antibody-forming cells and proliferative response to anti-CD3 antibody in rats (McAllister-Sistilli et al. 1998).

Human Studies

Studies of the effects of tobacco smoke on immune function and host defenses can be broadly grouped as those focusing on markers in peripheral blood, serologic responses to specific antigens, and markers in specimens obtained by bronchoalveolar lavage.

Studies of immune response markers in peripheral blood to acute respiratory infections are summarized in Table 4.2. However, the interpretive value of many of these studies is limited by insufficient information on the sources and health status of the participants. Of the studies noted in Table 4.2, only those by Gulsvik and Fagerhol (1979), Tollerud and colleagues (1989), Senior and colleagues (1991), Kurtti and colleagues (1997), and Sankilampi and colleagues (1997) are based on population samples with clearly defined criteria for assessing the health status of smokers and nonsmokers. Torres and colleagues (1998) also examined population samples in an effort to assess clinical characteristics of COPD patients with community-acquired pneumonia. The remaining studies have small sample sizes and the sources of the participants are not always clear. Although innumerable studies have observed differences in peripheral white blood cell counts in smokers as compared with nonsmokers, the consequences of this increase remain unclear, especially because few data exist on the effects of smoking on *peripheral phagocytic and immune-competent cells.*

Inconsistent findings in studies observing exposure-response relationships based on the amount of smoking may reflect varying definitions of smoking and the small numbers of persons in some of the studies. Even among those studies that were population-based or those that were larger, exposure-response relationships have not been consistently demonstrated (Gulsvik and Fagerhol 1979; Petitti and Kipp 1986; Tollerud et al. 1989b).

Nasal mucociliary clearance is probably important in the clearing of microorganisms from the nasopharynx. A study of the rate of nasociliary clearance found the rate of clearance to be delayed in smokers (20.8 [standard deviation = 9.3] minutes versus 11.1 [standard deviation = 3.8] minutes in nonsmokers). In this study the beat frequency of the cilia was not affected in smokers, and this finding suggests that the slower clearance is due either to a loss of cilia and/or changes in the viscoelastic properties of nasal mucus caused by cigarette smoke (Stanley et al. 1986). A study of bacterial adherence to buccal cells found that Streptococcus pneumoniae (S. pneumoniae) but not Hemophilus influenzae (H. influenzae) had an increased adherence in cigarette smokers. Since bacterial adherence to the cell is the first step in the colonization of bacteria, this finding may indicate an important mechanism for enhancing bacterial colonization and infection in smokers (Platt et al. 1997).

Although smoking generally seems to suppress immune function, the evidence does not suggest particular mechanisms by which smoking might act to increase the risk of an acute infection (Table 4.2). One possible mechanism relates to the effect of cigarette smoke on the enhancement of IgE immunoglobulin responses through effects on interleukin-4 (IL-4) production by CD4 lymphocytes (Byron et al. 1996). IgE levels tend to be higher in smokers than in nonsmokers, and the production of serum IgE is increased in cigarette smokers. Suppression of IL-4 may shift the response away from a Th-2 type response, characterized by the production of interferon, IL-2, tumor necrosis factor alpha, and IL-12 that lead to phagocytosis and the destruction of microbial pathogens (Arrand and Lucksley 1996; Lucksley et al. 1996). As a result, smoking may enhance the ability of common respiratory microbial pathogens (e.g., viruses) both to infect the host and decrease the host's ability to control the infection.

Studies of markers in bronchoalveolar lavage specimens provide additional insights into how exposure to tobacco smoke could alter host defenses and increase morbidity from acute infections (Table 4.3). Moreover, the differences in marker profiles (e.g., distribution of CD4 and CD8 T lymphocytes) between peripheral blood and bronchoalveolar lavage data suggest that both systemic and pulmonary responses need to be evaluated to assess the effects of smoking on host defenses against respiratory pathogens. New data from bronchoalveolar lavage studies also suggest that smoking can alter regulation of the cytokine network. Increased production in smokers of the cytokine IL-1 by alveolar macrophages may be responsible for decreased levels of serum immunoglobulins and decreased antibody responses to vaccines because of IL-1's role in the production of light chains in B cells (Yamaguchi et al. 1989). The suppression of regulatory cytokines IL-1 receptor antagonist and IL-6 (Mikuniya et al. 1999), the inhibition of the chemotactic factor inactivator by tobacco smoke, and the increase in numbers of neutrophils in the lung (Robbins et al. 1990; Costabel et al. 1992; Repine et al. 1997) could contribute to a heightened inflammatory response that increases morbidity and/or mortality from a respiratory infection.

In summary, since the last Surgeon General's reports to address the topic (USDHHS 1988a, 1990), new evidence has emerged buttressing the biologic basis of how cigarette smoking could increase the risk of and morbidity from acute respiratory infections: (1) animal data on the inhibitory effects of nicotine on T cell receptor stimulation indicate a plausible basis for the decreased mitogenic responses observed in smokers; (2) bronchoalveolar lavage fluid in smokers shows a more proinflammatory cytokine profile than in nonsmokers, suggesting that dysregulation of the cytokine network and inhibition of inflammation regulators provide a basis for more severe inflammation in smokers with respiratory infections; and (3) the emergent understanding of the role of Th-1 and Th-2 lymphocyte phenotypes on immune responses to foreign antigens indicates that the capacity of cigarette smoke to skew immune responses to a Th-2 phenotype could play a role in host responses to an infection. These immunologic alterations can be expected to increase the risk of acute infections through various effects on pulmonary airways, including decreased ciliary function and impaired mucociliary clearance (Janoff et al. 1987), and metaplastic changes in the airway epithelium (Sherman 1992) that diminish the capacity of physical clearance mechanisms.

Table 4.2 Studies on the effects of smoking on markers of human immune function and host defenses, derived from analyses of peripheral blood

Marker	Findings in smokers compared with nonsmokers
White blood cell counts (WBCs)	Higher total WBC (Silverman et al. 1975; Miller et al. 1982; Tollerud et al. 1989a) • differential count may not be altered (Tollerud et al. 1989a) • questionable relationship to the amount smoked (Tollerud et al. 1989b) • In African Americans, lymphocyte increases were greater than increases in PMNs* (Tollerud et al. 1991) • overall increase was less in African Americans than in Hispanics and Asians (Miller et al. 1982; Tollerud et al. 1989a)
Effect [illegible] cell type	Increase in total number of lymphocytes (Silverman et al. 1975; Miller et al. 1982; Cosio et al. 1978) • no increase in overall percentage (Silverman et al. 1975) • some studies have observed lower CD8 and higher CD8 rates (Miller et al. 1982; Tollerud et al. 1989a; Tollerud et al. 1991; Senior et al. 1991) but other studies (Senior et al. 1991; Kurtti et al. 1997) • [illegible] CD4/CD8 [illegible] (Tollerud et al. 1989b; Miller et al. 1991) except in African Americans (Tollerud et al. 1991) Decrease in NK cells (Silverman et al. 1981; Tollerud et al. 1989a; Melska et al. 1989; Senior et al. 1991; Sherman et al. 1991) Higher [illegible] counts in some studies (Miller et al. 1991; Tanigawa et al. 1993) PMN [illegible] (Tollerud et al. 1989b)
Cellular function	Higher activity [illegible] • no effect on the PMN phagocytic index or on myeloperoxidase levels; minimal effect on reduction after an acute exposure (Corberand et al. 1979) • decreased activity in the chemotactic factor inactivator in vitro (Robbins et al. 1990) • decreased leukocyte migration (Johnson et al. 1990) Lymphocyte function • effects on mitogenic responses to phytohemagglutinin/concanavalin A were variable (Daniele et al. 1977; Petersen et al. 1983; Melska et al. 1989) • reversible decreases in NK function (Johnson et al. 1990; Melska et al. 1989) • in vitro nicotine inhibition of NK function (Natr et al. 1990)
Immunoglobulin (Ig)	Increased serum IgE, IgA, and IgM concentrations (Gulsvik and Fagerhol 1979; Melska et al. 1989; McMillan et al. 1988) Higher [illegible] (Tollerud et al. 1989a)

*PMN = polymorphonuclear neutrophil leukocytes.
†NK = natural killer.

Table 4.2 Continued

Marker	Findings in smokers compared with nonsmokers
Serologic responses to specific antigens	Bacterial antigens • no association of IgG titers with pneumococci in the elderly, but titers to Hemophilus influenzae (H. influenzae) and Moraxella catarrhalis were higher (Kurtti et al. 1997) • reversible increases in antibody concentrations to the common cell-wall polysaccharide of pneumococcal types 6A and 8 (Sankilampi et al. 1997) Viral antigens • a higher H. influenzae titer response to natural influenza infection but a lower response to vaccination (Fiddes et al. 1971a) • no effect on H. influenzae and single radial diffusion titers from 2 strains of influenza virus (Macnicol et al. 1978) • no evidence for a decrease in response to influenza vaccination in persons aged ≥65 years (Powell et al. 1999)
Other	• An increased risk of cerebrospinal fluid bacterial meningitis in smokers (Brouwer et al. 1998)

smoke on the enhancement of IgE immunoglobulin responses through effects on interleukin-4 (IL-4) production by CD4 lymphocytes (Byron et al. 1996). IgE levels tend to be higher in smokers than in nonsmokers, and the production of serum IgE is increased in cigarette smokers. Suppression of IL-4 may shift the response away from a Th-2 type response, characterized by the production of interferon, IL-2, tumor necrosis factor alpha, and IL-12 that lead to phagocytosis and the destruction of microbial pathogens (Arrand and Lucksley 1996; Lucksley et al. 1996). As a result, smoking may enhance the ability of common respiratory microbial pathogens (e.g., viruses) both to infect the host and decrease the host's ability to control the infection.

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In summary, since the last Surgeon General's reports to address the topic (USDHHS 1988a, 1990), new evidence has emerged buttressing the biologic basis of how cigarette smoking could increase the risk of and morbidity from acute respiratory infections: (1) animal data on the inhibitory effects of nicotine on T cell receptor stimulation indicate a plausible basis for the decreased mitogenic responses observed in smokers; (2) bronchoalveolar lavage fluid in smokers shows a more proinflammatory cytokine profile than in nonsmokers, suggesting that dysregulation of the cytokine network and inhibition of inflammation

Table 4.3 Studies on the effects of smoking on markers of human immune function and host defenses, derived from analyses of bronchoalveolar lavage fluid

Marker	Findings in smokers compared with nonsmokers
Distribution of cell types (other than macrophages)	• Lower CD4, higher CD8, and lower CD4/CD8 counts not found in blood (Costabel et al. 1986; Yamaguchi et al. 1989; Mikuniya et al. 1999) • Higher numbers of alveolar macrophages (Hoh 1987; Yamaguchi et al. 1989; Mikuniya et al. 1999) • Higher numbers of [illegible]
Cellular function	[illegible] • [illegible] • [illegible] • [illegible] • [illegible] • [illegible]

regulators provide a basis for more severe inflammation in smokers with respiratory infections; and (3) the emergent understanding of the role of Th-1 and Th-2 lymphocyte phenotypes on immune responses to foreign antigens indicates that the capacity of cigarette smoke to skew immune responses to a Th-2 phenotype could play a role in host responses to an infection. These immunologic alterations can be expected to increase the risk of acute infections through various effects on pulmonary airways, including decreased ciliary function and impaired mucociliary clearance (Janoff et al. 1987), and metaplastic changes in the airway epithelium (Sherman 1992) that diminish the capacity of physical clearance mechanisms.

Acute Respiratory Infections in Persons Without Chronic Obstructive Pulmonary Disease

Epidemiologic Evidence

Influenza Infections

Some of the earliest studies of the effects of cigarette smoking on acute respiratory infections focused on the influenza virus (Table 4.4). Studies have shown an increased incidence of clinical influenza illness and infection in young, healthy smokers when compared with young, healthy nonsmokers (Pinkerton et al. 1969,

Table 4.4 Studies on the association between smoking and the occurrence of influenza virus illness and infection

Study/method	Findings	Comments
Finklea et al. 1969 Surveillance of 1,900 male cadets after the 1968 Hong Kong A_2 influenza epidemic at a South Carolina military academy included – standardized questionnaire serology and virus isolation – outcomes based on influenza symptoms and bed rest – smoking by category and number of cigarettes/day (never smokers; former cigarette, pipe, or cigar smokers; [illegible] smokers of 1–20 [illegible] or >20 cigarettes [illegible])	• Compared with nonsmokers – heavy smokers (≥20 cigarettes/day) had 21% more illnesses and 20% more bed rest – light smokers (<20 cigarettes/day) had 10% more illnesses and 7% more bed rest • Smoking had no effect on severity as measured by ratio of illness to bed rest • The number of cadets with hemagglutination inhibition (HI) titers >40 increased – [illegible] heavy smokers = 53% – clinically well smokers were more likely to have titers >40 than clinically well never smokers [illegible]	Findings were adjusted for important confounders (e.g., socioeconomic class, vaccination status); population was homogeneous by age, gender, and race; OR* for heavy vs. never smokers for illness was 1.52 and for bed rest 1.33 (based on percentages given in the text – actual numbers were difficult to determine); overall conclusion is that clinical and subclinical illnesses increased but severity did not
Finklea et al. 1971 [illegible]	[illegible] smokers had fewer responses to vaccination [illegible] prevaccination [illegible]	Findings were adjusted for important confounders [illegible]

*OR = Odds ratio.

Table 4.4 Continued

Study/method	Findings	Comments
Kark and Lebiush 1981 Surveillance of a 1979 outbreak at a military base for women in Israel (n = 176) – retrospective assessment of illness with standardized questionnaire – ill persons were identified as nonsmokers (never and former smokers) or current smokers (occasional and regular smokers)	• Risk of influenza-like illness among current smokers compared with nonsmokers – OR = 1.44 (95% CI†, 1.03–2.01) – 60.0% in current smokers vs. 41.6% in nonsmokers • Current smokers sought medical attention more frequently than nonsmokers (38.9 vs. 14.9%) but had no difference in [illegible] of illness‡ • Population attributable risk (PAR) estimate was 13% [illegible]	Study group selection was based on high morbidity in the unit; unknown biases were associated with the selection process; PAR estimates have limited utility and suggest a small effect; retrospective assessments of illness were not verified; PAR estimate did not specifically account for smoking prevalence (34.6%)
Kark et al. 1982 [illegible]	[illegible]	[illegible]

†CI = Confidence interval.
‡Severity of illness was defined as mild (returned to duty after visiting the clinic) or severe (hospitalized at the base or released from duty but not bedridden).

Table 4.4 Continued

Study/method	Findings	Comments
Petitti and Friedman 1985b Stratified random sample of smokers and simple random sample of never smokers from current larger study based on a U.S. health maintenance organization database, 4,610 current smokers and 2,035 never smokers (6,645) enrolled between July 1979 and December 1983 – standardized questionnaire for tobacco tar yield was based on the 1978 Federal Trade Commission report – medical record reviews – outcomes were based on acute respiratory d[illegible] pneumonia/influenza [illegible] chronic obstructive pulmonary disease [illegible]	• Smokers of low-tar vs. high-tar yield cigarettes had no underlying COPD; other findings included – OR (pneumonia/influenza) = 0.9/5 mg decrease in tar (95% CI, 0.7–1.0) – effects were not seen in smokers of a single brand • Smokers of low-tar yield cigarettes vs. never smokers – OR (pneumonia/influenza) = 1.7 (95% CI, 1.0–3.0) – no control for underlying COPD	No effects were seen for the broad category of acute respiratory infections (International Classification of Diseases 460–466); analyses were adjusted for age, gender, race, and number of cigarettes/day; the use of nonstandardized medical records is a serious limitation; age distribution was not provided
Cruijff et al. 1999 Double-blind [illegible] trial of [illegible] in persons aged [illegible] years from 31 general medical practices in the Netherlands during the 1991–1992 influenza season – a questionnaire was used to obtain smoking history and occurrence of influenza – 321 smokers and [illegible] nonsmokers [illegible] sized as none, light (1–[illegible] cigarettes/day), moderate (10–19 cigarettes/day), or heavy (≥20 cigarettes/day) – serology	• No significant differences [illegible] [illegible]	[illegible]

1971a; Kark and Lebiush 1981; Kark et al. 1982). An attributable risk of 31.2 percent (95 percent confidence interval [CI], 18.5–43.1) was reported for clinical influenza in U.S. male military recruits in a closed outbreak environment (Kark et al. 1982). The data for the severity of an illness are less clear, with studies of young, healthy persons providing conflicting results (Table 4.4) (Finklea et al. 1969; Kark et al. 1982). The evidence on smoking and influenza-like illnesses in older populations is even more limited. A randomized, placebo-controlled Dutch trial of influenza vaccines in persons aged 60 years and older (Cruijff et al. 1999) did not show an increase in clinical disease among smokers, but did show an increase in asymptomatic (by serology) infections in smokers in the placebo arm of the trial (the odds ratio [OR] adjusted for age, gender, and an underlying risk group = 1.61 [95 percent CI, 0.91–2.83]). A study of adults (age distribution not given) from a health maintenance organization in the United States found an increased OR for a physician/nurse practitioner visit for pneumonia/influenza (no distinction made) among smokers of high-tar cigarettes compared with low-tar cigarette smokers (Table 4.4) (Petitti and Friedman 1985b). Unfortunately, the study depended on a medical record review of practitioner diagnoses, with no criteria in the report as to how the "pneumonia/influenza" diagnosis was assigned. Without these criteria, it is difficult to interpret the OR of 1.7 (95 percent CI, 1.0–3.0) for the occurrence of illness in smokers of low-tar cigarettes compared with nonsmokers, since this analysis was not adjusted for the presence of COPD in the smokers.

Whether smokers have an increased risk of infection with influenza viruses in contrast to more often having a clinically recognizable illness remains clouded. A study of healthy U.S. military cadets found evidence of increased asymptomatic infections among smokers in addition to a larger percentage of smokers with high hemagglutination inhibition (HI) titers (≥1:40) to influenza A (Finklea et al. 1969, 1971a). As a group, however, ill smokers tended to have lower HI titers to influenza A_2 than ill lifetime nonsmokers, after adjusting for the effects of illness and vaccination status. Ill smokers also had higher titers to influenza B but poorer responses to vaccination with influenza B antigen. Overall responses to vaccination with influenza A and B antigens did not differ among various smoking groups and lifetime nonsmokers. However, smokers had a decreased persistence of antibody at a one-year follow-up evaluation. In the Dutch study of persons aged 60 years or older (Cruijff et al. 1999), smoking status was inversely related to the likelihood of a serologic infection among those who were vaccinated—possibly because smokers develop a better immunologic protection after vaccination than nonsmokers—but showed a direct relationship in those who received a placebo (Table 4.4). These findings do not suggest that smokers are less responsive to the beneficial effects of influenza vaccination, at least in the elderly.

Pneumonia and Infections with Pathogens that Infect the Lower Respiratory Tract

Several well-designed and well-executed U.S. population-based studies have provided evidence of a link between cigarette smoking and acute lower respiratory tract infections (Table 4.5). A population-based, case-control study of 205 cases of community-acquired pneumonia (Almirall et al. 1999a,b) reported an attributable risk of 23.0 percent (95 percent CI, 3.3–42.7) for a history of ever smoking. An exposure-response relationship based on the number of cigarettes smoked per day was observed in former smokers, who had an adjusted OR close to that of current smokers of 10 to 20 cigarettes per day (Table 4.5). The Centers for Disease Control and Prevention sponsored a case-control study of invasive pneumococcal disease based on a population surveillance system (Nuorti et al. 2000). Although the number of cases for which pneumonia was the underlying source of the invasive disease was not given, pneumonia is likely to have been the main diagnosis in the 216 (out of a total sample of 228) cases in patients with bacteremia. The population attributable risk estimate for smoking was 51 percent (no CIs were given), compared with 14 percent for chronic illnesses. The authors estimated that reducing the prevalence of smoking to 15 percent among persons aged 18 through 64 years would prevent 4,000 cases per year of invasive pneumococcal disease in the United States. Of particular interest in this study was the observation that after 10 years of smoking cessation, the risk of invasive pneumococcal disease reached that of nonsmokers.

Serologic evidence of infection with *Chlamydia pneumoniae* (*C. pneumoniae*) was evaluated in a sample from the European Respiratory Health Survey (Table 4.5) (Ferrari et al. 2000). The adjusted OR as evidence of recent infection (IgG titer >512 or IgM titer >16) with *C. pneumoniae* in smokers compared with nonsmokers was 3.51 (95 percent CI, 1.26–9.67). Finally, a matched, case-control study of community-acquired infections with *Legionella pneumophila* was carried out with cases derived from a prospective pneumonia surveillance system in the United States (Table 4.5) (Straus et al. 1996). The univariate OR for infection in current

smokers compared with nonsmokers was 3.75 (95 percent CI 2.27–6.17). However, in a multivariable logistic regression model, an effect from current smoking was observed only in those patients with no evidence of an underlying disease (OR = 7.49 [95 percent CI, 3.27–17.17]).

A study of Finnish twins (all zygosities) discordant for smoking reported that male current and former smokers were more likely to have evidence of ongoing infections with *C. pneumoniae* (IgA titer >40) than their male twins who had never smoked (Table 4.5) (von Hertzen et al. 1998a,b). Antigen-specific lymphocyte responses to *C. pneumoniae*, but not to other *Chlamydia* antigens, also were decreased in the male smokers (von Hertzen et al. 1998b). No effects were observed in female twins. The authors interpreted the lymphocyte data as being consistent with Th-2 skewing of the immune response in males. The gender differences in these responses are not explained.

Data from several different types of studies have suggested a link between smoking and infection with *Mycobacterium tuberculosis* (Table 4.5). A study of one million deaths from 1986–1990 in 98 urban and rural areas of China estimated that 11.3 percent of deaths from tuberculosis could be attributed to smoking (Table 4.5) (Liu et al. 1998). Exposure-response

Table 4.5 Studies on the association between smoking and the occurrence of pneumonia and infection with pathogens that infect the lower respiratory tract

Study/method	Findings	Comments
	Population-based samples	
Straus et al. 1996 Cases (n = 146) of community-acquired *Legionella* identified as part of a prospective pneumonia surveillance from 15 hospitals in 2 Ohio counties from December 1990–October 1992 • cases were matched to 2 hospital controls (by gender, age, and underlying disease) standardized questionnaire standardized home survey	• Univariate OR* for current smoking = 3.75 (95% CI[†], 2.27–6.17) compared with nonsmokers – OR = 2.21 (95% CI, 1.51–3.21)/packs/day • In multivariable models, smoking had an effect only in cases without an underlying disease – adjusted OR = 7.49 (95% CI, 3.27–17.17)	None
Wo[illegible] Random sample [illegible] atch [illegible]	[illegible] her patie [illegible]	[illegible]

*OR = O[illegible]
[†]CI = Confidence interval.

Table 4.5 Continued

Study/method	Findings	Comments
	Population-based samples	
Liu et al. 1998 Study of smoking histories for 1 million persons who died between 1986 and 1988, in 98 urban and rural areas in China – smoking histories were obtained from next of kin and friends (rural only) – smoking histories were available only up to 1980 – deaths were identified from death certificates and medical record reviews	• 11.3% of tuberculosis deaths in men were attributed to smoking; 2.8% in women (smoking prevalence was very low in women) • Exposure-response relationship, based on the number of cigarettes/day in both urban and rural environments for urban male smokers vs. nonsmokers – risk ratios for 1–19, 20, >20 cigarettes/day = 1.24, 1.48, and 2.03, respectively • Exposure-response relationship based on age when smoking began – risk ratios for urban male smokers (began at age <20 years, 20–24 years, ≥25 years) vs. nonsmokers were 1.86, 1.4[illegible] and 1.2[illegible] respectively	Small subsample to validate smoking histories by spouses (major source of data)
Almirall et al. [illegible] Population-based matched (gender and age) case-control study [illegible]	• OR for pneumonia compared with nonsmokers [illegible] • EF [illegible] • Effects of the number of cigarettes [illegible] – former smokers [illegible]	The analysis [illegible] whose illness met the case definition [illegible] pneumonia [illegible] findings [illegible] confirmed [illegible] were [illegible] EF which [illegible] from the [illegible] were sensitive to [illegible] factors [illegible] a vari[illegible] disease [illegible] use)

[illegible]
[‡]COPD = Chronic obstructive pulmonary disease.
*PAR = Population attributable risk.
[§]Miettinen's EF = CF_1 multiplied by EF, where CF_1 = case fraction in the higher risk category.

Table 4.5 Continued

Study/method	Findings	Comments
	Population-based samples	
Ferrari et al. 2000 Participants were adults aged 20–44 years from the European Respiratory Health Study [illegible] – standar[illegible] with [illegible] smoking – serol[illegible] antib[illegible] – C. [illegible] antigens were used as controls	• OR for recent infections in smokers of 20 cigarettes/day = 3.51 (95% CI, 1.26–9.67) compared with nonsmokers – 25.7% of all smokers compared with 9.9% of nonsmokers had evidence of recent infections	Analyses were controlled for gender, occupation, socioeconomic class, education, and family size; IgG antibody >512 or IgM >16 was interpreted as evidence of a recent infection
Nuorti et al. 2000 Population-based, active surveillance system in Atlanta (Georgia), Baltimore (Maryland), and Toronto (Canada) – 25% sample (n = 228) of invasive pneumococcal infections in nonimmunocompromised persons aged 18–64 years, studied between January 1995 and May 1996 – standardized interviews – 301 controls obtained by random-digit telephone dialing	• Adjusted OR for current smok[illegible] • Adjusted OR for current smok[illegible] • Exposure-response relationship [illegible] pack-years** • PAR [illegible]	Only [illegible]

*PAR = Population attributable risk.
**Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Table 4.5 Continued

Study/method	Findings	Comments
	Case-control studies	
Buskin et al. 1994 Case-control study at a tuberculosis clinic in Seattle, Washington, 1988–1990 newly diagnosed cases of tuberculosis (n = 151) controls (n = 545) from the same clinic – standardized questionnaire – smoking status and cigarettes/day	• No exposure-response relationship with the number of cigarettes/day • Adjusted OR (for age and alcohol use) for smoking duration compared with controls – 20–29 years: 1.8 (95% CI, 0.7–4.[illegible]) – ≥30 years: 2.6 (95% CI, 1.[illegible])	69% of eligible cases participated; 63% of eligible controls participated; alcohol use and smoking were correlated but no data were given; numbers were too small to evaluate smoking effects in nondrinkers
Alcaide et al. 1996 [illegible]	• Adjusted OR for smoking = [illegible] • Exposure-response relationship [illegible] • Miettinen's EF[§] [illegible]	[illegible]

[§]Miettinen's CF = CF_1 multiplied [illegible] where CF_1 = case fraction in the higher risk category.

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Table 4.5 Continued

Study/method	Findings	Comments
Case-control studies		
Anderson et al. 1997 Inmates in South Carolina prisons who had data on tuberculosis status at intake and who were re-evaluated in a 1990 survey – endpoint: skin test conversion – case (converter, n = 118/141) – control frequency matched by race (n = 127/182) – medical records – computerized data reviewed from computerized inmate records – questionnaire on smoking habits	• Adjusted OR (race, age, gender, and prison living conditions) for conversion among smokers compared with nonsmokers – number of cigarettes/day since incarceration – 1–10: 1.88 (95% CI, 0.96–3.69) – >10: 1.87 (95% CI, 0.92–3.78) – cigarettes/day before incarceration – 1–20: 1.32 (95% CI, 0.76–2.31) – >20: 1.75 (95% CI, 0.83–3.71) – duration of smoking (referent: never/former) – 1–15 years: 1.60 (95% CI, 0.81–3.16) – >15 years: 2.12 (95% CI, 1.03–4.36)	82% participation by cases; 70% participation by controls; prisoners who smoked before incarceration decreased their smoking in prison, but the authors could not explain this decrease; the authors suggest that an association between long duration of smoking and decreased mucociliary clearance can explain the effects of duration and the current amount of smoking
Twin studies		
[illegible]	[illegible]	[illegible]

relationships with the number of cigarettes smoked per day and time since onset of smoking were observed in both urban and rural environments. However, a survey of the occurrence of positive tuberculin skin tests in a large nursing home population in Hong Kong (Woo et al. 1996) failed to find an association with smoking (Table 4.5). In contrast, three case-control studies provided evidence of an association. A nonpopulation-based, case-control study in Spain evaluated smoking as a risk factor for newly diagnosed tuberculosis (Table 4.5) (Alcaide et al. 1996), and found an estimated attributable risk of 48 percent (95 percent CI, 13–69). Moreover, the authors observed a strong exposure-response relationship with the number of cigarettes smoked per day and an additive effect from passive exposure to tobacco smoke. Two other case-control studies in the United States (both in Washington state) demonstrated associations between the duration of smoking and risk for newly diagnosed tuberculosis (Buskin et al. 1994) and skin test conversion (Anderson et al. 1997), but no association with the current number of cigarettes smoked per day (Table 4.5).

Acute Upper and Lower Respiratory Illnesses with and Without Identification of Specific Pathogens

A large number of studies on the incidence of URI and LRI in relation to cigarette smoking were reviewed in the 1989 Surgeon General's report on smoking and health (USDHHS 1989), some of which are summarized in Table 4.6. Although not provided in the text of the papers, attributable risk estimates for the effects of smoking (Rockhill et al. 1998) can be calculated for several of the previously reviewed studies (Table 4.6) (Parnell et al. 1966; Finklea et al. 1971b; Monto et al. 1975; Blake et al. 1989). Attributable risk estimates of URI for smokers were similar in studies [illegible] gent populations: 31 percent (95 [illegible] student nurses (Parnell et al. [illegible] (95 percent CI, 12–30) and 29 percent (95 percent CI, 10–44) in two military trainee populations (Finklea et

Table 4.6 Studies on the association between smoking and the occurrence of acute upper respiratory illness (URI) and lower respiratory illness (LRI), with and without identification of specific pathogens

Study/method	Findings	Comments
Beake 1958 • 101 participants from 59 families who were part of a Western Reserve University family longitudinal study in Cleveland, Ohio – smoking groups were divided into never; 1–10, 11–20, or >20 cigarettes/day; and pipe and cigar smokers • Analysis of incidence from 1949–1954 and symptoms of – common respiratory diseases (cold, rhinitis, laryngitis, bronchitis, or pharyngitis) – specific respiratory diseases (streptococcal tonsillitis and pharyngitis, pneumonia, and influenza)	• Frequency of illness was not related to the amount smoked	The common respiratory diseases group comprised approximately 95% of the total respiratory illnesses found in the family study population; overall results do not show a consistent increase in frequency of illness or types of symptoms

Table 4.6 Continued

Study/method	Findings	Comments
Haynes et al. 1966 • 179 males aged 11–19 years from a Princeton, New Jersey, preparatory school • Smoking histories were recorded on a questionnaire – regular: ≥1 cigarette or pipe/day – heavy: >10 cigarettes/day for >1 year – occasional: ≥1 cigarette or pipe/week • Respiratory illness classifications were based on infirmary record entries (a need for antimicrobial therapy served as the distinguishing criterion between mild and severe respiratory infections) – (1) upper mild and (2) upper severe: sinusitis, rhinitis, pharyngitis, and laryngitis – (3) lower mild and (4) lower severe: tracheobronchitis, bronchitis, and pneumonia – (5) combined (upper and lower) mild – (6) combined (upper and lower) severe • Smoking habit and illness history questionnaire • 1-year period of observation (incidence)	• Increase in episodes/10 persons with increased smoking – exposure-response gradient from never to regular but not to heavy when all episodes were considered together – heavy smokers were 6.5 times more likely than nonsmokers (actual data were not given) to have a severe LRI and a LRI combined with URI; these findings were similar to findings comparing smokers and nonsmokers • Severe URI frequency was the same for occasional and regular smokers	Detailed age-adjusted data were not given; cannot compute actual RR* and AR† rates

*RR = Relative risk.
†AR = Attributable risk.

Table 4.6 Continued

Study/method	Findings	Comments
Parnell et al. 1966 • 47 current-smoking and 47 never-smoked student nurses in Vancouver, Canada, matched for time on pediatric duty (greatest probable exposure to upper respiratory tract infections), followed September 1963–August 1964 • Retrospective assessment of respiratory illnesses while working at the health service • 4 categories of illness – pure URI – tracheitis/bronchitis/pneumonia – coryza syndrome (could have LRI) – other	• Incidence (10^2) per 1,000 in smokers vs. nonsmokers – pure URI: 7.52 vs. 5.18 – tracheitis/bronchitis/pneumonia: 3.18 vs. 1.42 – coryza syndrome: 8.14 vs. 5.17 • There were no differences in severity	Selection of the sample and determination of smoking habits were performed independently of the surveillance to avoid bias; usual clinical records were used with no standardized data collection; true incidence rates were counted using proper person-time (for purposes of analysis, each person per unit of time); ARs‡ can be estimated from the data provided (AF§ [96] was calculated from [illegible] rates in Table [illegible] [illegible] all ARI* [illegible] [illegible] 44)¶ URI = [illegible] LRI = [illegible]
[illegible] • [illegible] cases in a military academy in North Carolina • Surveillance of illness during [illegible] URI (nasal stuffiness, pharyngitis, LRI (sputum, bronchitis, pneumonia) • Questionnaire on smoking habits was completed at the beginning of the school year (never, regular [≥1 cig/day], heavy [illegible] smoker [≥1 pack/day] cigarettes)	• Smokers had greater frequencies of URI (no exposure-response gradient was seen for cigarettes/day) • Smokers had a greater frequency of URI than the [illegible] (exposure-response gradient was seen for cigarettes/day) • Several [illegible] other illnesses [illegible] smoking	Data were used [illegible] assuming [illegible] AF [illegible] calculated from [illegible] in Table [illegible] [illegible] [illegible] of adjusted [illegible] were considered LRI [illegible] LRI [illegible]

†AR = Attributable risk.
‡AF = Attributable fraction.
§ARI = Acute respiratory illness.
¶CI = Confidence interval.
#Confidence intervals were calculated with "ipitab" of STATA 6.0 for incidence density and cumulative incidence data, where appropriate. Confidence intervals for rate fractions are only approximate, since actual person-time data were not available.

Table 4.6 Continued

Study/method	Findings	Comments
Monto et al. 1975 • Family selection in Tecumseh, Michigan, was based on the occurrence of chronic bronchitis (CB) or low FEV_1** in a member, matched with families without CB • 290 men, 293 women, 266 children • Studies of health and disease in Tecumseh began in 1957, and 3 series of examinations of the residents took place in 1959–1960, 1962–1965, and 1967–1969 • Families were followed for 1 year (incidence) • Persons were studied at baseline, 6 months, and 12 months • Family histories of respiratory infections were recorded on questionnaires • Serologic blood testing • Weekly contacts by phone to detect a respiratory illness—if reported within 2 days of onset, specimens for isolation were obtained	• Annual cumulative incidence of serologically proven infection with influenza A and B; respiratory syncytial virus; parainfluenza 1, 2, and 3; *Mycoplasma pneumoniae*; and coronavirus OC43 – higher among smokers in all categories for males and females – 9.9% among male smokers vs. 4.4% among male nonsmokers – 11.1% among female smokers vs. 9.4% among female nonsmokers	Data and evaluation were restricted to healthy members of control households (i.e., no CB or low FEV_1); no adjustment for age, age range was 16 years and older; data can be used to compute ARs[†] (AF[‡] [%] was calculated for healthy persons from cumulative incidence data in Table 5, Monto et al. 1975, combined across partic[illegible] groups: ma[illegible] 0-77; [illegible] female [illegible] -55 to 54)[§]; 2 subsequent publications reported that stratification by CB eliminated differences in male smokers (Monto and Ross 1977, 1978); RR was approximately 1.4 for females in both strata
Pollard et al. 1975 • Naval recruits from [illegible] 1971–January 1972 in Orlando, Florida • 1096 sample [illegible] records from infirmary: [illegible] sample of [illegible] ,554 • Ques[illegible] [illegible] at the beginning and end of [illegible]	• [illegible] no differences [illegible] • [illegible]	[illegible]

[*]AR = Attributable risk.
[†]AF = Attributable fraction.
[‡]Confidence inte[illegible] were calculated with "Epitab" of STATA 6.0 for incide[illegible] [illegible]sity and cumulative incidence data, where appropri[illegible]. Confidence intervals for rate fractions are only approx[illegible], since actual person-time data were not available.
**FEV_1 = Forced expiratory volume in 1 second.

Table 4.6 Continued

Study/method	Findings	Comments
Aronson et al. 1982 • 867 walk-in patients (534 females, 333 males) from 2 health maintenance organizations in Providence, Rhode Island, and Boston, Massachusetts, and 2 hospital-based practices; December 1976–November 1977 – limited to chief complaints of coughing, chest congestion, head or neck swollen glands, difficulty swallowing, or sore throat • Classified as URI, LRI, or laryngopharnygeal	• Female patients had age-adjusted OR[‖] = 2.65 (95% CI, 1.97–3.80) for smoking • Smokers were more likely than nonsmokers to have LRI (57 vs. 45%) – greater duration of coughing: 8.9 vs. 6.8 days – exposure-response relationship was found between the amount smoked and number of days of coughing (never smoked, 6.8 d[illegible]; <1 pack/day, 7.7 d[illegible]; ≥1 pack/d[illegible], [illegible]4 days); no age or gender differ[illegible]	Methods for data collection and verification of smoking status were not given; a nonstandard data collection method was probably used
Blake et al. 1988 • [illegible] • [illegible]	• [illegible] – [illegible] – [illegible] • [illegible] • [illegible] ARI[§]	[illegible]

[*]AR = Attributable risk.
[†]AF = Attributable fraction.
[§]ARI = Acute respiratory illnesses.
[‡]Confidence intervals were calculated with "Epitab" of S[illegible] for in[illegible]ce density and cumul[illegible] incidence data, where appropriate. Confidence intervals for rate fractions are only app[illegible]mate, since actual pers[illegible] time data were not available.
[‖]OR = Odds ratio.

Table 4.6 Continued

Study/method	Findings	Comments
Cohen et al. 1993 • 154 men, 263 women (volunteers) in Salisbury, England, who received an intranasal challenge with rhinovirus types 2, 9, or 14 respiratory syncytial virus; or coronavirus 229E – aged 18–54 years – infection was defined as virus isolation or [illegible]logic response at 28 days post inoculation • Smoking only by status: smokers (average cotinine ≥15 ng/mL) or nonsmokers [illegible]	• Development of colds – nonsmokers: 38% – 1–15 cigarettes/day: 40% – >15 cigarettes/day: 48% • Adjusted OR for smokers vs. nonsmokers = 2.03 (95% CI, 1.18–3.70) • Negative interaction with alcohol (i.e., smoking reversed the [illegible] association between alcohol and colds)	Controlled for alcohol use, prior serologic status (serologically positive for rhinoviruses [antibody titer >2]), rooming with an infected person, gender, and allergy history
Jaakkola and [illegible] • 393 [illegible] • [illegible] • Standar[illegible]	• [illegible]	[illegible]
Nicholson et al. [illegible] • Prospective weekly follow-up of Leicester, England, community sample of persons during the winters of [illegible] and 1993–1994 • 60–90 years of age (n = 533) • Virus isolation and serology • Standardized questionnaire was used to obtain information	• Cur[illegible] [illegible]rmer, smoke[illegible] had an increased risk of complicated LRI compared with [illegible] smokers – inca[illegible], need to see medical doctor, hospitalization – logistic regression: OR for current smoking and complications = 1.47 (95% CI, 1.14–1.90)	There were data on th[illegible] [illegible] relationship between smoking and the occurrence of respiratory infections

al. 1971b; Blake et al. 1988). A similar coherence was found for LRI (Table 4.6) (Parnell et al. 1966; Finklea et al. 1971b). In the Tecumseh, Michigan, population-based cohort study (Monto et al. 1975), smokers tended to have a higher incidence of serologically determined infections (Table 4.6).

Of three studies published since the 1990 report, two supported an association between smoking and acute respiratory illnesses (Table 4.6) (Cohen et al. 1993; Nicholson et al. 1996). The third study, which did not support this association (Jaakkola and Heinonen 1995), was based entirely on self-reported illnesses. A study of volunteers who received an intranasal challenge with rhinovirus and coronavirus (Table 4.6) (Cohen et al. 1993) found an adjusted OR for infection in smokers compared with nonsmokers (virus isolation or serologic response at 28 days) of 2.03 (95 percent CI, 1.18–3.70). A prospective study of a community sample of people aged 60 through 90 years (Nicholson et al. 1996) reported an adjusted OR associated with current smoking for complicated LRI of 1.47 (95 percent CI, 1.14–1.90).

Acute Respiratory Infections in Persons with Human Immunodeficiency Virus Infection

Respiratory infections are a main source of morbidity in persons with human immunodeficiency virus (HIV) infection. Several studies have evaluated cigarette smoking and risk for incident lower respiratory infections in persons infected with HIV (Table 4.7).

A large observational cohort study with up to four years of follow-up found a CD4-adjusted relative hazard (RH) for bacterial pneumonia in HIV-infected current smokers of 1.57 (95 percent CI, 1.14–2.15) (Table 4.7) (Burns et al. 1996). No excess risk from tuberculosis or infection with *Pneumocystis carinii* (*P. carinii*) was observed. A second cohort study did not find an excess risk of bacterial pneumonia in HIV-infected patients who smoked when compared with infected patients who did not smoke (Hirschtick et al. 1995). However, among HIV-infected patients with a CD4 count below 200/mm³, smokers had an incidence of pneumonia more than three times higher (13.8/100 person-years compared with 4.0 in nonsmokers) (Table 4.7). A cross-sectional study of a variety of infections within the past six months in HIV-positive and HIV-negative women with similar characteristics based on self-reporting documented an OR for pneumonia in smokers of 2.7 (95 percent CI, 1.2–5.8) (Table 4.7) (Flanigan et al. 1999). No other infections were associated with smoking. A study based on a retrospective evaluation of medical records found that the median time from the onset of HIV infection to a clinical infection with *P. carinii* was significantly shorter in smokers (9 months) than in nonsmokers (16 months) (Nieman et al. 1993). Smoking did not appear to affect the time of onset of acquired immunodeficiency syndrome (AIDS) for non-*Pneumocystis* AIDS-defining conditions.

Evidence Synthesis

Since the publication of the 1990 Surgeon General's report (USDHHS 1990), the biologic basis for evaluating associations between cigarette smoking and acute respiratory infections has been strengthened, adding to the plausibility of an association of smoking with respiratory infection. Animal studies on the effects of nicotine demonstrate a mechanism for immune suppression. The effects of cigarette smoke on the regulation of the cytokine network and in producing a Th-2 bias in lymphocyte responses to antigens imply that smokers will have an increase in inflammation and a decrease in protective host responses to infections with respiratory pathogens.

A review of the evidence across all of the studies indicates that cigarette smokers, particularly current smokers, have an increased risk for an acute URI or LRI. The findings are generally consistent among studies and some provide evidence for dose-response with amount of smoking. When persons are classified as current or former smokers or lifetime nonsmokers, ORs generally have been above 1.5 for acute respiratory infections in smokers without an underlying illness compared with nonsmokers (Tables 4.4 through 4.6). However, ORs as high as seven have been reported in at least one well-conducted study of *Legionella* infection (Straus et al. 1996). The few studies that focused on persons with HIV infection documented a similar range of excess infection rates (Table 4.7). When current smokers are classified by the number of cigarettes smoked per day, exposure-response relationships have been found in some studies. The lack of a standardized measure for current smoking makes the comparison of estimates from various studies difficult. Lower tar content of cigarettes is associated with a decrease in the incidence of acute respiratory illnesses (Petitti and Friedman 1985b), consistent with the exposure-response relationship observed with the amount smoked each day and with population-based studies showing a decreased incidence in former smokers when compared with current smokers (Almirall et al. 1999a,b; Nuorti et al. 2000). A range of potential confounding factors has been considered across the studies.

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The evidence is less clear as to whether the risk associated with smoking varies for lower versus upper respiratory infections. In studies reporting an excess incidence of lower respiratory infections, infections tended to be in the heaviest smokers. Studies of military populations have produced conflicting results. A single study of persons aged 60 years or older (Nicholson et al. 1996) indicated that smokers were more likely than nonsmokers to have a complicated LRI.

Finally, the available data do not provide a basis for identifying subgroups particularly susceptible to the smoking-induced risks of acute respiratory illnesses. Studies of HIV-infected persons suggest that the incremental incidence of disease is similar to that in non-HIV-infected people. One study did provide evidence that the effects of smoking on acute respiratory illnesses might be greatest in those most severely immunocompromised (Hirschtick et al. 1995).

Table 4.7 Studies on the association between smoking and the occurrence of acute respiratory infections in persons with human immunodeficiency virus (HIV) infection

Study/method	Findings	Comments
Nieman et al. 1993 84 cases of HIV infection from a pool of 516 cases in London, England, who were assessed from 1986–1991 before the onset of acquired immunodeficiency syndrome (AIDS), for progression time to AIDS in relation to smoking habits – retrospective assessment of medical records – nonstandardized periodic follow-up	• Median time of progression to AIDS from HIV infection was 8.17 months for smokers vs. 14.5 months for nonsmokers median time to *Pneumocystis carinii* pneumonia (PCP) onset was 9 months for smokers vs. 16 months for nonsmokers (significant by log rank test) – smoking had no effect on onset time to non-PCP AIDS • Distribution of stages at presentation was similar for smokers and nonsmokers	A major problem is the lack of data on the duration of infection before the first HIV test; results could all be due to longer duration of infection in smokers; no data were given on CD4 counts
Hirschtick et al. [illegible] Cohort of 1,136 HIV-positive and 187 HIV-negative participants from a multicenter study (San Francisco [illegible], Chicago, Detroit, San [illegible] and Newark [illegible] enrolled [illegible] December 1985–[illegible] 1991 – [illegible] 21 follow-up [illegible] – standard protocols were used for evaluation at follow-up – outcome [illegible] pneumonia based [illegible] – smoking class[illegible] never, current, former	• Smoking [illegible] was associated with [illegible] occurrence of [illegible] after adjusting for [illegible] [illegible] and sampling with [illegible] [illegible] and [illegible] • Subjects [illegible] were [illegible] among people with [illegible] [illegible] – [illegible] [illegible] per person-years [illegible] – smokers: [illegible] per person-years [illegible]	In different [illegible] never-smokers with [illegible] cases, [illegible] was 2.4 (95% CI, 2.3–4.9)[1]

CI = Confidence interval.
[1]Calculation is based on data available in the report [illegible] It is only approximate, since actual person-time data (each person[s] per unit of time, in this [illegible] were not available [Hirschtick et al. 199[illegible]

Table 4.7 Continued

Study/method	Findings	Comments
Burns et al. 1996 Observational cohort of 3,221 HIV-positive persons, from 17 clinics in a community network in 13 U.S. cities, enrolled from September 1990–November 1992 – all with baseline CD4 measurements – standardized data collection was used in all of the clinics – follow-up was twice a year for up to 4 years – outcome: various indices of disease progression – smoking classifications were never, current, and former – number of cigarettes/day was obtained only at baseline	• There was no overall association of smoking with respiratory disease progression or death • Current smokers had an increased risk of bacterial pneumonia compared with never smokers – adjusted relative hazard (RH) of 1.57 (95% CI, 1.14–2.15) – similar risk among persons with CD4 levels above and below 200/mm[3] • Current smokers showed no excess risk for tuberculosis compared with never smokers (RH = 1.17 [95% CI, 0.58–2.36]) • Results were not affected by various stratified analyses used to evaluate both confounding and interaction • No exposure-response relationships with the number of cigarettes smoked	Careful attempts was made to identify confounders (CD4 count, other drugs, therapy, previous HIV progression, care, and functional status); the effects of changes in smoking behaviors over the follow-up period were not studied; 25 conditions were evaluated with the RH of smoking above and below 1 (e.g., cryptococcal infections)
Thurgan et al. 1995 Cross-sectional analysis of a multicenter US cohort of HIV-positive (HIV+) and HIV-negative (HIV−) women at risk for HIV infection (with [illegible] risk factors) [illegible] Rhode Island, Baltimore, Maryland and Detroit, Michigan – [illegible] reported history of [illegible] diagnosis of tuberculosis, pneumonia, or recurrent [illegible] and sinusitis	• Adjusted [illegible] to a self-reported [illegible] [illegible] [illegible] the [illegible] [illegible] smokers [illegible]	No control [illegible] [illegible] [illegible] [illegible] HIV-related risk factors [illegible] HIV-positive and HIV-negative [illegible] model [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible] [illegible]

Conclusion

1 The evidence is sufficient to infer a causal relationship between smoking and acute respiratory illnesses, including pneumonia, in persons without underlying smoking-related chronic obstructive lung disease.

Implications

There are numerous studies providing population attributable risk estimates of the effects of smoking on respiratory illness outcomes (Table 4.8). Two of these estimates [illegible] limited generalizability because they [illegible] selected military populations (Kark and [illegible] 1980; Kark et al. 1980). The estimate based on [illegible] cases of invasive pneumococcal disease (Nuorti et al. 2000) is [illegible] useful, because it has been assumed that [illegible] of the cases studied the disease originated in the respiratory tract. Although this assumption is reasonable given the particular bacterium, no data on this point were given. Nonetheless, the 51 percent estimate indicates a large contribution to disease burden in the populations studied. The remaining estimates in Table 4.8 are the attributable fractions for smokers. Excluding the estimate with CIs including 1, estimates ranged from 18 to 63 percent. Because the various estimates are based on incidence density data as well as on cumulative incidence data, it is not possible to give a unifying interpretation (etiologic or excess fraction) for all of the estimates (Greenland and Robins 1988). However, considering all of these estimates as "excess" cases (Greenland 1989) of acute respiratory illness provides a maximum estimate of the excess burden that smoking imposes on the occurrence of these illnesses. In most cases, the estimated amount of excess cases is greater than 20 percent.

From a public health standpoint, an argument could be made that additional studies on the broad question of smoking and acute respiratory illnesses are not needed. However, studies to assess the economic and social impacts of this association may still be useful, particularly if they establish common definitions of and criteria for acute respiratory conditions and smoking status. Ideally, these studies should provide data detailing current smoking patterns and smoking patterns for the five years before the study. Using open populations in these studies should make estimates of both population and smoking attributable fractions possible. Such studies must be large enough to provide precise estimates of these fractions and to take into account whatever confounders may be relevant. Small studies are not likely to be useful. National studies, such as the National Health and Nutrition Examination Survey, would be an ideal venue for addressing these components.

Finally, in the context of health care services, health care providers need to make all smokers aware of the implications of these data for their health. The effects of smoking on the incidence of acute respiratory diseases should be included in all health care messages to smokers.

Acute Respiratory Infections in Persons with Chronic Obstructive Pulmonary Disease and Asthma

Epidemiologic Evidence

The population-based Tecumseh study was one of the most extensive epidemiologic investigations examining the effects of cigarette smoking on acute respiratory infections in persons with and without chronic lung disease in the United States (Monto et al. 1975; Monto and Ross 1977, 1978). This multiyear study recruited several stratified random samples of families. During a one-year period, people participated in weekly telephone interviews to identify prospectively the occurrence of an acute respiratory illness. Each participant also underwent serial clinical, spirometric, and serologic examinations. Two definitions of an acute respiratory infection were used: self-reported acute respiratory symptoms and serology (a fourfold rise in serum antibody titer to selected respiratory pathogens).

The observed association between current smoking and self-reported acute respiratory infections was addressed in a series of study reports (Table 4.9). The small sample sizes in subgroups resulted in wide CIs, complicating the interpretation of results. However, smoking has been associated with an increased risk for several indexes of illness: acute respiratory infections in healthy men, based on both self-reported and serologic evidence of infection (Monto et al. 1975); serologic evidence of respiratory infections in women with or without chronic bronchitis (Monto and Ross 1978); and acute, self-reported lower respiratory tract infections in men, especially in those with chronic bronchitis (Monto and Ross 1977). However, not all of the analyses found smoking to be associated with a higher risk of acute respiratory infections in persons with chronic bronchitis (Table 4.9).

In the Tecumseh study, COPD, as indicated by chronic bronchitis or pulmonary function impairment, was itself associated with a greater risk of developing

Table 4.8 Estimates of attributable risk fractions for smoking and acute respiratory illness (ARI) in persons without chronic obstructive pulmonary disease

Study Population	Type of risk estimate*	Estimate (95% CI*)
Parnell et al. 1986 • Incidence data from student nurses	• Attributable fraction – all ARI – upper respiratory illness (URI) – lower respiratory illness (LRI)	39% [illegible], 32–44) [illegible] [illegible]
Hinkley et al. 1987b • Medical care utilization [illegible] • Noninfluenza [illegible]	• Attributable fraction [illegible] [illegible] days – URI – LRI	[illegible] [illegible] [illegible]
Monto et al. 1975 • Serious respiratory illness • Serological [illegible] illness	• Attributable fraction men women	34% (95% CI, [illegible]) [illegible]
Kark and Lebiush 1981 • Hospitalized cases • Influenza-like illness	Population attributable risk (PAR)	[illegible]
Kark et al. 1980 • Mild illness episodes • Influenza-like illness	• Risk all nonmilitary influenza influenza – adjusted risk [illegible] [illegible] [illegible]	[illegible] (95% CI, 27.5–37.9) [illegible] (95% CI, [illegible]–43.1)
Fuller et al. 1988 • Airway narrowing • URI [illegible] symptoms	Attributable fraction	[illegible]
Alcais et al. 1986 • Cases [illegible] [illegible] allergic [illegible]	Etiologic fraction	45% (95% CI, 13–69)
Adams et al. 1986a,b • Population-based [illegible] • Pneumonia	Etiologic fraction	[illegible]
Nuorti et al. 2000 • Population surveillance • Invasive pneumococcal disease	PAR	51% (no CI given)

*All terms used, except "attributable fraction," are those of the author of the specific study. Estimates labeled "attributable fraction" were calculated only from studies that provided complete data from clearly defined source populations in addition to sufficient primary data.
CI = Confidence interval.

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an acute respiratory infection (Table 4.10), although the effects of smoking were stronger and more consistent among men. In men, the risk varied with the number of cigarettes smoked and the presence of chronic bronchitis, with the risk of an acute respiratory illness highest in heavy smokers of more than one pack per day with chronic bronchitis (relative risk [RR] = 1.63), followed by moderate smokers of approximately one and one-half packs per day (RR = 1.45), and nonsmokers (RR = 1.15). (The smoking categories were based on the sum of three reports measuring the number of cigarettes smoked per day: none equals zero packs, category 1 equals less than one pack, category 2 equals one to one and one-half packs, and category 3 equals one and one-half packs or more per day; moderate smokers were in the four to six packs category and heavy smokers were in the seven to nine packs category.) This pattern was not apparent in women.

Many studies have documented a high prevalence of potentially pathogenic bacteria isolated from the sputum of persons with an exacerbation of COPD (Tager and Speizer 1975; Fagon et al. 1990; Murphy and Sethi 1992; Menso et al. 1995; Murphy et al. 2000; Voelkel and Tuder 2000). In most studies, the specific role of current cigarette smoking in acute infections was not examined. Sofer and colleagues (1998) used bronchoscopy with a protected specimen brush to examine bacterial infections in 50 patients with severe COPD exacerbations requiring mechanical ventilation. The prevalence of a positive culture for gram-negative bacilli, including *Pseudomonas* species, was similar in former and current smokers (23 percent versus 32 percent). In contrast, a study of 81 ambulatory patients with an acute exacerbation of COPD demonstrated an association between current smoking and a greater risk for a quantitative sputum culture yielding *H. influenzae* (OR = 8.16 [95 percent CI, 1.9–43]) (Miravitlles et al. 1999).

A population-based, cross-sectional study from Norway examined the association between a clinical diagnosis of obstructive lung disease (COPD or asthma) and serologic evidence of a respiratory viral infection (influenza A and influenza B viruses, parainfluenza virus types 1–3, adenovirus, and respiratory syncytial virus [RSV]) (Omenaas et al. 1996). The prevalence of a positive serology, indicating recent or past infections, was higher among persons with obstructive lung disease (74 percent) than among those with chronic respiratory symptoms (60 percent) or persons who were asymptomatic (48 percent). Compared with persons without evidence of infections, those with positive serology for RSV and influenza B virus had lower standardized forced expiratory volume in one second (FEV_1) residuals (-0.61 and -0.54, respectively). For these viruses, an exposure-response relationship was observed between viral titers and FEV_1 residuals. The association between a positive RSV serology and FEV_1 residuals was of a greater magnitude in smokers (-0.93) than in former smokers (-0.65) or nonsmokers (-0.48), although the interaction between smoking and RSV infections was not significant. The investigators observed a similar pattern of results for influenza B virus serology (-1.02 among smokers, -0.46 among former smokers, and -0.30 among nonsmokers). Analyses were not carried out to assess the interaction between the joint effect of having obstructive lung disease and smoking, which would directly address the risk posed by smoking for viral infections among persons with COPD. The cross-sectional design precludes determining whether a viral infection reduces lung function or whether decreased lung function increases susceptibility to viral infections.

The impact of smoking on the risk of death from pulmonary infections among persons with COPD was examined in the population-based Copenhagen City Heart Study (Prescott et al. 1995). In the cohort of 13,888 persons followed for 10 to 12 years, 214 persons died from COPD (8 percent of deaths). Of these deaths, 133 occurred in the hospital. Medical records were reviewed for 101 patients to determine whether death was due to a pulmonary infection. Compared with persons who died without pulmonary infections (n = 51), those who died from a pulmonary infection (n = 38) had similar smoking statuses. Both groups also had similar prevalence rates of current smoking (75 percent of those without pulmonary infection versus 82 percent of those with infection) and current heavy smoking (53 percent for both), and a similar mean duration of smoking (36 years versus 40 years). In a Cox proportional hazard model that controlled for age, gender, and FEV_1, daily tobacco use was related to the risk of death from a pulmonary infection (RH = 1.4 per 10 grams of tobacco used; 95 percent CI, 1.04–1.80). When current smokers and lifetime nonsmokers were compared, smoking was not associated with an increased risk. Although a selection bias from examining a subset of COPD deaths cannot be excluded, the data strongly suggest a relationship between current smoking intensity and the risk of death from a pulmonary infection.

A population-based, case-control study demonstrated that cigarette smoking was a strong risk factor for invasive pneumococcal disease (Nuorti et al. 2000). Moreover, both COPD and asthma were associated with a greater risk of pneumococcal infection (OR = 3.4 [95 percent CI, 1.6–7.0] and OR = 2.5 [95 percent

Table 4.9 Studies on the association between smoking and the risk of acute respiratory illness (ARI)—Results from the Tecumseh Study

Study	Population	RR[a] and 95% CI[b]
		Men
Monto et al. 1975	• Stratified random sample of families followed during 1967–1969, containing 1 member with chronic lung disease: symptomatic CB[c] or low FEV_1[d] without symptoms (presumed emphysema) • Comparison groups were healthy persons and persons with other chronic illnesses (diabetes, coronary [illegible]	RR for current smoking vs. never or former smoking[e] • Self-reported ARI – persons with CB: 0.84 – low FEV_1: 1.08 – healthy persons: 1.79 – other chronic illnesses: 1.64 • Serologic definition of ARI[f] – persons with CB: 1.74 (95% CI, 0.74–5.02) – low FEV_1: 0.83 (95% CI, 0.41–1.68) – healthy persons: [illegible] (95% CI, [illegible]) – other chronic illnesses: [illegible] (95% CI, 0.05–8.47)
Monto and Ross 1978	Stratified random sample of families followed during 1969–1971	[illegible] • Heavy smoking vs. none: 0.89 • Moderate smoking vs. none: 1.08 • Light smoking vs. none: 0.91 • All current smokers vs. none: [illegible] persons with and without CB – persons with CB: 0.71 – persons without CB: 0.91 Self-reported ARI (lower tract only) • Heavy smoking vs. none: 0.73 • Moderate smoking vs. none: 1.38 • Light smoking vs. none: 0.68 • All current smokers vs. none: [illegible] persons with and without CB – persons with CB: 0.81 – persons without CB: 0.90

[a] RR = relative risk.
[b] CI = Confidence interval.
[c] CB = Chronic bronchitis.
[d] FEV_1 = Forced expiratory volume in 1 second.
[e] Relative risks were calculated using STATA 5.0 "Epitab" function. Confidence intervals were calculated where adequate data in the publication were available.
[f] Serologic definition of an acute infection = a 4-fold rise in serum antibody titer to respiratory syncytial virus, parainfluenza virus type 3, influenza A virus, influenza B virus, or *Hemophilus influenzae*.
[g] Cigarette smoking was assessed 3 times during the study year. No smoking was assigned a score of 0; smoking <1 pack/day = 1; 1 pack but <1.5 packs/day = 2; and ≥1.5 packs/day = 3. A summary score was created by adding the 3 individual scores. Using the summary score, 0 = nonsmoking, 1–3 = light smoking, 4–6 = moderate smoking, and 7–9 = heavy smoking.

RR and 95% CI	
	Women
RR for current smoking vs. never or former smoking	
• Self-reported ARI	
– persons with CB: 0.72	
– low FEV_1: 1.05	
– healthy persons: 1.02	
– other chronic illnesses: 1.46	
• Serologic definition of an ARI	
– persons with CB: 1.10 (95% CI, 0.32–3.62)	
– low FEV_1: [illegible] (95% CI, 0.16–2.51)	
– healthy persons: [illegible] (95% CI, 0.41–2.14)	
– other chronic illnesses: [illegible] (CI undefined)	
Self-reported ARI (total)	
• Heavy smoking vs. none: 1.05	
• Moderate smoking vs. none: 1.01	
• Light smoking vs. none: 0.86	
• Any current smoking vs. none in persons with and without CB	
– persons with CB: 0.81	
– persons without CB: 0.90	
Self-reported ARI (lower tract only)	
• Heavy smoking vs. none: 1.38	
• Moderate smoking vs. none: 1.38	
• Light smoking vs. none: 1.13	
• Any current smoking vs. none in persons with and without CB	
– persons with CB: 1.0	
– persons without CB: 1.29	

CI, 1.4–4.7]), respectively. In a multivariate analysis that included smoking variables and demographic characteristics, neither disease was associated with a greater risk of pneumococcal infection. Other investigators also found that COPD was associated with a greater risk of pneumococcal pneumonia and bronchitis (RR = 1.98 [95 percent CI, 1.51–2.56]) (Simberkoff et al. 1986).

A recent report from the Lung Health Study evaluated the effects of the frequency of self-reported nonspecific LRI that resulted in a visit to a physician on the annual rate of change in FEV_1 levels in participants with mild COPD (Kanner et al. 2001). The number of illness episodes was few in this population, averaging about 0.24 per year for the study population as a whole. Illnesses in the year before the study and female gender were the best predictors of subsequent illnesses, but these two variables explained only 8.4 percent of the total variation. However, during the five-year observation period, participants who were continuous smokers had significantly more illnesses than those who had quit smoking for the entire five-year period ($p = 0.0003$). Intermittent smokers had illness rates that fell between the continuing smoker and sustained quitter groups. In this study, nonspecific lower respiratory tract illnesses that resulted in a physician visit had an adverse effect on the annual rate of change in lung function only in those who continued to smoke. The illness effect on changes in the FEV_1 was not seen in sustained quitters (Kanner et al. 2001).

Evidence from Antibiotic Trials

The potential etiologic role of smoking in acute respiratory infections among persons with COPD can be assessed indirectly by examining data from clinical trials of the efficacy of antibiotic treatments for acute exacerbations of COPD. If a bacterial infection plays an important causal role in the acute exacerbation of COPD, characterized by increases in coughing, sputum production, wheezing, dyspnea (difficulty breathing and shortness of breath), and/or airflow obstruction, then treatment with appropriate antibiotics should accelerate symptomatic resolution. Current smoking might decrease the efficacy of antibiotic therapy, and past smoking might influence the risk for infections by determining the level of lung function. This section considers the evidence from trials of antibiotics in exacerbations of COPD. These trials are potentially informative as to the role of bacteria in causing these exacerbations and whether current smoking modifies the effects of antibiotics. Furthermore, they offer evidence on the role of bacteria in causing

Table 4.9 Continued

Study	Population	RR[a] and 95% CI[b]
		Men
Monto and Ross 1978	Stratified random sample of families followed during 1969–1971	Self-reported ARI • Persons with CB[c] – heavy smoking vs. none: 0.96 – moderate smoking vs. none: 0.91 • Persons without CB – heavy smoking vs. none: 0.73 – moderate smoking vs. none: 0.68 Serologic definition of ARI: current smokers vs. nonsmokers • Persons with CB: [illegible] (95% CI, [illegible]) • Persons without CB: [illegible] (95% CI, [illegible]) • Both groups (total): [illegible] (95% CI, [illegible])

[a] RR = relative risk.
[b] CI = Confidence interval.
[c] CB = Chronic bronchitis.

the exacerbations and provide insights into a causal pathway that begins with smoking, is followed by the onset of COPD, and finally leads to an increased risk for a bacterial infection. However, these studies do not address the role of viruses, which cause the majority of acute upper respiratory infections in the general population.

Beginning in 1957, randomized placebo-controlled clinical trials have examined the efficacy of antibiotics in acute exacerbations of chronic bronchitis characterized by coughing, sputum production, wheezing, or dyspnea (Table 4.11). Studies have examined patients hospitalized for acute exacerbations of chronic bronchitis (Elmes et al. 1965; Petersen et al. 1967; Pines et al. 1968, 1972; Nicotra et al. 1982) and persons treated as outpatients (Elmes et al. 1957; Berry et al. 1959; Fear and Edwards 1982; Anthonisen et al. 1987; Jorgenson et al. 1992; Sachs et al. 1995). Except for one single-blind study (Petersen et al. 1967), all trials were double-blind. Several trials demonstrated that antibiotic treatments reduced respiratory symptoms (Elmes et al. 1957; Anthonisen et al. 1987), physician assessed clinical severity (Berry et al. 1959; Pines et al. 1968, 1972), work loss (Elmes et al. 1957), and sputum purulence (Pines et al. 1972). Other trials found that antibiotic treatment improved peak expiratory flow rates (Elmes et al. 1965; Anthonisen et al. 1987). Conversely, other clinical trials showed no effects of antibiotics on respiratory symptoms (Fear and Edwards 1982; Sachs et al. 1995), clinical severity (Elmes et al. 1965; Jorgensen et al. 1992), sputum volume or purulence (Elmes et al. 1965; Petersen et al. 1967; Nicotra et al. 1982), or peak expiratory flow or other pulmonary function testing (Petersen et al. 1967; Pines et al. 1972; Nicotra et al. 1982; Jorgenson et al. 1992; Sachs et al. 1995).

In a randomized controlled trial that has been widely cited, Anthonisen and colleagues (1987) tested three different antibiotic treatments (trimethoprim-sulfamethoxazole, ampicillin, or doxycycline) against a placebo. In contrast to earlier studies, all patients had a clinical diagnosis of COPD and a FEV_1/forced vital capacity (FVC) ratio of less than 70 percent. Nearly all patients had a history of smoking cigarettes (95 percent), with 21 percent indicating current smoking. After two weeks of standard treatments for COPD, patients received an antibiotic or placebo for acute exacerbations characterized by increased dyspnea, sputum volume, and sputum purulence. In the trial, 173 patients had 362 exacerbations. Treatment success, defined as symptom resolution within 21 days, was significantly more apparent in the antibiotic group than in the placebo group (68 percent versus 57 percent of exacerbations). The duration of antibiotic-treated exacerbations was also shorter (average 12 days vs. [illegible]). When the analysis was restricted to first exacerbations, the results were similar. Increases in peak expiratory flow rates were also greater in patients treated with antibiotics.

In the largest clinical trial, Jorgenson and colleagues (1992) randomly assigned 278 general practice patients with acute exacerbations of chronic

RR and 95% CI	Women
Self-reported ARI	
• Persons with CB	
– heavy smoking vs. none: 0.80	
– moderate smoking vs. none: 0.78	
• Persons without CB	
– heavy smoking vs. none: 0.81	
– moderate smoking vs. none: 0.92	
Serologic definition of ARI, current smokers vs. nonsmokers	
• Persons with CB: [illegible]	
• Persons without CB: [illegible]	
• Both groups (total): [illegible]	

bronchitis to amoxicillin or a placebo. Smoking history was not reported. Based on blinded physician assessments, there were no differences in clinical outcomes between the amoxicillin (63 percent) or placebo (64 percent) groups after eight days. Although peak expiratory flows improved in all patients, there were no differences between the groups.

These studies are limited by a small sample size and low statistical power, which likely reduced the ability to detect antibiotic efficacy. One study of hospitalized patients included patients with radiographic infiltrates, suggesting pneumonia (Elmes et al. 1965); other studies of inpatients did not explicitly exclude persons with pneumonia (Petersen et al. 1967; Pines et al. 1968). Inclusion of patients with pneumonia would likely inflate the apparent efficacy of antibiotics in acute COPD exacerbations. Although most patients with chronic bronchitis have smoked cigarettes, most studies do not report smoking histories (Elmes et al. 1957, 1965; Petersen et al. 1967; Pines et al. 1968; Fear and Edwards 1982; Petersen et al. 1967; Elmes et al. 1972; Nicotra et al. 1982; Anthonisen et al. 1987; Jorgensen et al. 1992). Even if the efficacy of antibiotics were to suggest that smoking plays a causal role in acute bacterial infections, none of the studies separated remote effects from immediate effects of cigarette smoking on the risk of infection. Remote effects of smoking on acute respiratory infections are those mediated through chronic airway obstruction, mucous hypersecretion, and impaired mucociliary clearance; immediate effects are the alteration of immune and inflammatory functions (USDHHS 1990).

The limitations of low study power were addressed by a meta-analysis that combined 11 of the randomized controlled trials (Elmes et al. 1957, 1965; Barry et al. 1980; Fear and Edwards 1982; Petersen et al. 1967; Pines et al. 1968, 1972; Nicotra et al. 1982; Anthonisen et al. 1987; Jorgensen et al. 1992; Sachs et al. 1995). Because the studies used many different outcome measures, Saint and colleagues (1995) calculated a standardized effect size. The overall summary effect size, which was the difference between mean outcomes in the antibiotic and placebo groups divided by the pooled standard deviation, was 0.22 (95 percent CI, 0.10–0.34), indicating a small benefit from antibiotics. Combining the six trials that measured peak expiratory flow rates yielded a summary improvement of 10.75 liters per minute with antibiotic treatments (95 percent CI, 4.96–16.54 liters per minute).

Observational data also support the efficacy of antibiotics in treating acute exacerbations of COPD. A nonrandomized clinical trial examined the efficacy of cefaclor in 106 outpatients with acute exacerbations of chronic bronchitis (Cazzola et al. 1981). In this trial all patients were current cigarette smokers, and potentially pathogenic bacteria were isolated from the sputum of most participants. On the basis of clinical examinations, the majority of patients were considered to be cured (75.5 percent) or improved (17 percent). There was no significant change in pulmonary function. A major limitation of this trial is the absence of a placebo control group. Taken together with randomized trials, this trial suggests the efficacy of antibiotics for current smokers with acute exacerbations of chronic bronchitis.

A cohort study examined 173 patients who had 362 emergency department visits for acute exacerbations of COPD during an 18-month period (Adams et al. 2000). For patients to be included, the investigators required evidence of airway obstruction verified by pulmonary function testing during the previous three years. Of 1,754 patient visits to the emergency department for an acute COPD exacerbation, 1,392 were excluded. The most common reason for exclusion was no record of recent pulmonary function testing (1,122 visits). Although antibiotics were prescribed preferentially to patients with more severe exacerbations, antibiotic administration was associated with a lower proportion of recurrent emergency department visits during the ensuing 14 days (19 percent versus 27 percent, $p < 0.001$). Active cigarette smoking was associated with a greater risk of relapse (OR = 1.45 [95 percent CI, 2.09–10.13]), which suggests that smoking may increase the severity of an acute exacerbation. Selection bias, introduced by excluding many emergency

Table 4.10 Studies on the association between smoking, chronic obstructive pulmonary disease, and the risk of acute respiratory illness (ARI)—Results from the Tecumseh Study

Study	Relative risk (RR) and confidence interval (CI)* Men	Women
Monto and Ross 1977	Total ARI (self-reported) • Chronic bronchitis (CB) vs. none: 1.48	Total ARI (self-reported) • CB vs. none: 1.1
	Lower respiratory illness (LRI) (self-reported) • CB vs. none: [illegible]	LRI (self-reported) • CB vs. none: 1.5
Monto and Ross 1978	Total ARI (self-reported) • CB vs. none: 1.45	Total ARI (self-reported) • CB vs. none: 1.29
	LRI (self-reported by reading intensity) • Heavy smoking: 1.66 • Moderate smoking: 1.16 • None: 1.15	LRI (self-reported by reading intensity) • Heavy smoking: 1.18 • Moderate smoking: 1.10 • None: 1.52
	Low FEV1 (spirometry) • Self-reported ARI: 1.5 • Serologically confirmed ARI (respiratory infection): 2.1 (95% CI: 1.2–3.4)	Low FEV1 (spirometry) • Self-reported ARI: 1.52 • Serologically confirmed ARI (respiratory infection): 1.2 (95% CI: 0.6–2.5)

*Relative risks were calculations using 1.0 as the reference value. Confidence intervals were calculated where adequate data in the publication were available.
†Cigarette smoking was assessed 3 times during the study period. No smoking was assigned a score of 0; smoking < 1 pack/day = 1; 1 pack but < 1.5 packs/day = 2; and ≥ 1.5 packs/day = 3. A summary score was created by adding these individual scores. Using the summary score, 0 = nonsmoking, 1–2 = light smoking, 4–6 = moderate smoking, and 7–9 = heavy smoking.
‡FEV1 = Forced expiratory volume in 1 second.
§Serologic definition of an acute infection = a 4-fold rise in serum antibody titer to respiratory syncytial virus, parainfluenza virus type 3, influenza A virus, influenza B virus, or *Hemophilus influenzae*.

department visits by patients without recent pulmonary function testing, limits any conclusions based on this study.

Prevention of COPD Exacerbation. Randomized trials of antibiotic prophylaxis in patients with COPD, conducted mostly in the 1950s and 1980s, provide evidence on cigarette smoking and the risk of respiratory infections in persons with chronic lung disease. If data indicate that antibiotics could prevent exacerbations of COPD, the indication would be that bacterial infection plays a role in COPD exacerbation. Because smoking is the principal cause of COPD, smoking would then have been shown to act on the causal pathway to acute bacterial respiratory infections in this patient group.

Placebo-controlled, randomized clinical trials have tested a variety of antibiotics, including tetracycline, sulfonamides, and combination agents (Table 4.11). Duration of treatment with antibiotics was administered for 1 to 20 months, with treatment in most trials lasting 1 to 6 months during the winter months (Nicotra et al. 1982; Burchann et al. 1958; Chetwick et al. 1959; Francis and Spicer 1960; Pirdie et al. 1962; Davis et al. 1961, 1965; Francis et al. 1961; Johnston et al. 1961, 1969; Fear and Edwards 1982; Medical Research Council 1966; Pines 1967; Llippo et al. 1987). Only three trials reported smoking status: 78 to 85 percent ever smoked, and 29 to 79 percent were current smokers (Medical Research Council 1966; Johnston et al. 1969; Llippo et al. 1987).

Of the various study outcomes examined, preventive antibiotics have demonstrated the most consistent efficacy in reducing missed workdays among persons with chronic bronchitis (Table 4.12). In two early large-scale, well-conducted clinical trials, Francis and Spicer (1960) and Francis and colleagues (1961) demonstrated that the prophylactic administration of tetracycline decreased the number of lost workdays by about 50 percent. The benefits of penicillin were less clear. A later clinical trial conducted by the Medical Research Council (1966) of Great Britain also suggested that oxytetracycline reduced the duration of missed workdays (22 percent reduction, 95 percent CI, 55 percent reduction to 4 percent increase, but the CI did not exclude a lack of benefit). Smaller or less well-controlled trials suggested that antibiotic prophylaxis reduced lost workdays (Pirdie et al. 1960; Johnston et al. 1961, 1969).

The salutary impact of prophylactic antibiotics on other clinical outcomes has been less consistent. Some clinical trials demonstrated that preventive antibiotics reduced acute exacerbations of chronic bronchitis (McVay and Sprunt 1953; Buchanan et al. 1958; Chetwick et al. 1959; Davis et al. 1961; Pines 1987), whereas others showed no benefit (Francis and Spicer 1960; Francis et al. 1961; Davis et al. 1965; Medical Research Council 1966; Johnston et al. 1969; Llippo et al. 1987). Despite reducing lost workdays, the two early British trials found that antibiotics did not reduce the incidence of symptomatic exacerbation, suggesting an effect mainly on symptom severity or duration (Francis and Spicer 1960; Francis et al. 1961). Although patients receiving prophylactic antibiotics may experience subjective (McVay and Sprunt 1953) or clinical improvements as determined by physicians (Fear and Edwards 1982), these benefits were not always observed (Davis et al. 1961, 1965; Johnston et al. 1961). In all trials that examined pulmonary function, antibiotics were not associated with any benefit (Francis and Spicer 1960; Pirdie et al. 1960; Davis et al. 1961, 1965; Medical Research Council 1966; Johnston et al. 1969; Llippo et al. 1987). Taken together, the conflicting evidence does not allow for a clear conclusion regarding the efficacy of prophylactic antibiotic interventions with COPD.

Randomized, placebo-controlled clinical trials tested the efficacy of an oral vaccination against formalin-killed [illegible] in patients with COPD (Fuglsang et al. 1989; Jorgensen et al. 1992; Tandon and Ghosh 1991). The results of these trials would support the efficacy of vaccination in acute exacerbations of COPD, with smoking acting on the causal pathway. Most persons in these trials reported having ever smoked cigarettes (78 to 91 percent), and fewer indicated current smoking (10 to 73 percent). In an early trial of 50 patients, Clancy and colleagues (1986) reported a tenfold reduction in the cumulative incidence of acute episodes of bronchitis after oral immunizations (6 percent in the placebo group versus 63 percent in the immunized group, RR = 0.10 [95 percent CI, 0.014–0.64]). The same investigators demonstrated in a subsequent controlled trial (n = 40) a reduction in episodes of acute wheezy bronchitis (30 percent versus 80 percent, RR = 0.38 [95 percent CI, 0.18–0.76]) and a decreased use of antibiotics (25 percent versus 60 percent, RR = 0.42 [95 percent CI, 0.18–0.96]) (Clancy et al. 1990). The study also suggested a reduction in the cumulative incidence of acute bronchitis exacerbations (60 percent versus 80 percent, RR = 0.63 [95 percent CI, 0.38–1.02]). Compared with the placebo group, the group that received oral vaccinations had no reductions in symptom duration or reports of dyspnea, and no improvement in FEV_1. The RRs and CIs for both studies by Clancy and colleagues (1985, 1990) were not published; the calculations were based on data available in the papers. A similar trial conducted in the highlands of Papua, New Guinea, enrolled 62 adults with chronic bronchitis (Lehmann et al. 1991). Oral vaccinations were associated with a reduced risk of acute bronchitis (RR for placebo group = 1.92 [95 percent CI, 1.58–2.26]). There was no impact on the risk of pneumonia (RR = 0.66 [95 percent CI, 0.23–1.09]). In a similar study of 84 persons with chronic bronchitis, an oral vaccination was associated with a reduced risk of acute lower respiratory tract infections (OR = 0.4 [95 percent CI, 0.2–0.9]) and improved general well-being assessed by a visual analog scale (median score 5.0 versus 2.6) (Tandon and Ghosh 1991).

Large-scale randomized controlled trials also have examined the efficacy of an oral vaccination with OM-85 BV, an antigenic extract of eight microorganisms commonly found in the respiratory tract that has been subjected to alkaline lysis. These agents are thought to activate lung macrophages and enhance antigen presentation to T lymphocytes (Collet et al. 1987). For the following studies, the RRs and CIs were calculated based on data available in the papers. In a study by Orcel and colleagues (1994), 334 adults aged 65 years or older with chronic bronchitis were randomly selected to receive OM-85 BV or a placebo. Of these patients, 51 percent had ever smoked and 25 percent were current smokers. Among the 280 patients analyzed, the cumulative incidence of acute lower respiratory tract infections was lower in the active treatment group (35 percent versus 62 percent, RR = 0.67 [95 percent CI, 0.51–0.88]). More recently, Collet and

Table 4.11 Studies on the efficacy of antibiotic treatment in acute exacerbations of chronic obstructive pulmonary disease

Study	N*	Smoking status	Antibiotic†
Elmes et al. 1957	88	NR‡	O
Barry et al. 1960	93	CH	[illegible]
[illegible]	67	NR	T
Elmes et al. 1965	56	NR	A [illegible]
Petersen et al. 1967	49	CH	CH
Pines et al. 1968	93	NR	[illegible]
Fin[illegible] 1972	229	NR	T or CH
[illegible]	40	[illegible]	T
Anthonisen et al. 1987	173	[illegible]	[illegible] or D
Jorgensen et al. 1992	275	NR	A [illegible]
Sachs et al. 1995	71	[illegible] 11% current smokers	A or C

*N = Total study size.
†O = oxytetracycline, A = ampicillin, CH = chloramphenicol, P = penicillin, S = streptomycin, T = tetracycline, TS = trimethoprim-sulfamethoxazole, D = doxycycline, C = co-trimoxazole.
‡All p values given are for between-group comparisons (antibiotic vs. placebo).
§NR = Data were not reported.
¶Refers to both the total number of exacerbations and the duration of each exacerbation.
**NS = Not significant.
††Trial was stopped early because of a high proportion who deteriorated in the placebo group.
‡‡FEV_1 = Forced expiratory volume in 1 second.

Main outcome measures	Findings (antibiotic vs. placebo)[a]
• Duration of [illegible] work [illegible]	24[illegible] vs. 528 (p = 0.1)
Physician [illegible]	
• [illegible]	[illegible]
• [illegible]	[illegible]
• [illegible]	[illegible]
• [illegible]	[illegible]
• [illegible]	No difference[illegible]
• [illegible]	[illegible]
• [illegible]	[illegible]
• [illegible]	[illegible]
• [illegible]	[illegible]
• [illegible]	[illegible]
• [illegible]	[illegible]
• [illegible]	[illegible]
	[illegible] vs. placebo
• [illegible]	[illegible]
• [illegible]	[illegible]
• [illegible]	[illegible] (p = NS)
• [illegible]	[illegible] (p = NS)
• [illegible]	[illegible] (p = NS)
• [illegible]	[illegible] (p = NS)
• [illegible]	[illegible]
• [illegible]	[illegible]
• [illegible]	[illegible] rates were [illegible] (p [illegible] 0.02)
• [illegible]	[illegible]
• [illegible]	[illegible]
	A vs. C vs. placebo
• [illegible] in peak flow per day (percent predicted)	0.58 vs. [illegible] (p = NS)
• Re[illegible] in symptom score per day	0.05 vs. [illegible] (p = NS)

Table 4.12 Studies on the efficacy of antibiotic preventive treatment of persons with chronic obstructive pulmonary disease

Study	N[a]	Subjects[b]	Duration of treatment	Smoking	Antibiotic[c]
McVay and Sprunt 1953	30	CB, E, B, or A	2 weeks–20 months	NR[e]	C and T
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	T
Cherniack et al. 1959	67	CB or B	3–18 months	NR	T OL and P P
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Pirdie et al. 1960	139	CB	24 weeks	NR	O P and SU
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Daily T, daily P, intermittent T, or intermittent P
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	PH
[illegible]	[illegible]	CB	[illegible]	[illegible]	[illegible]

[a]N = Total population size.
[b]CB = chronic bronchitis, E = emphysema, B = bronchiectasis, A = asthma.
[c]C = co-trimoxazole, T = tetracycline, OL = oleandomycin, P = penicillin, O = oxytetracycline, SU = sulphonamide, PH = phenethicillin, CH = chloramphenicol, SUL = sulphormethoxine, TR = trimethoprim.
[d]All p values given are for between-group comparisons (antibiotic vs. placebo).
[e]NR = Data were not reported.
[f]Fischer's exact test (2-sided) was calculated on the basis of published data.
[g]NS = Not significant.
[h]FEV_1/FVC = Forced expiratory volume in 1 second/forced vital capacity.

Main outcome measures	Findings (antibiotic vs. placebo)[d]
• Proportion developing fewer respiratory infections	81 vs. [illegible] = 0.004)[f]
• Hospitalization	9[illegible] (p = 0.14)
• Subjective improvement	80 [illegible]
Number of exacerbations (mean per year)	[illegible]
	T vs. OL and P vs. P vs. placebo
• Episodes of upper respiratory illness (mean)	[illegible] (p = NS[g])
• Episodes of lower respiratory illness (mean)	[illegible] <0.001 for T vs. [illegible]
• Vital capacity (mean change in percent predicted)	[illegible]
• FEV/FVC[h] (mean change)	[illegible] (p = NS)
[illegible] per person [illegible]	P vs. [illegible] placebo [illegible]
	[illegible] P and SU vs. placebo
• [illegible]	[illegible]
• Proportion [illegible]	[illegible]
• Propo[illegible]	[illegible]
• Days [illegible]	[illegible] (p = NS)
• [illegible]	[illegible]
• Subjec[illegible]	[illegible] 46.2% [illegible]
• Num[illegible]	[illegible]
• Char[illegible]	[illegible] (p = NS)
	Daily T vs. daily P vs. intermittent T vs. intermittent P
• Days of missed work (mean per 100 days)	[illegible] (p = 0.01 for daily T)
• Proportion taking additional antibiotics	[illegible]
• Visits to a general practitioner (mean number)	0.10 vs. [illegible] = NS)
• Workdays lost (mean per patient)	[illegible]
• Physician-assessed improvement	[illegible]
• Clinical score at 6 months, based on physician assessment and patient diary (mean)	159 vs. [illegible] (higher scores = better status)

Table 4.12 Continued

Study	N	Subjects[b]	Duration of treatment	Smoking	Antibiotic[c]
Davis et al. 1965	40	B	4–14 months	NR	CH
Medical Research Council 1966	[illegible]	CB	[illegible]	[illegible] smoked [illegible]	[illegible]
[illegible]	[illegible]	CB	[illegible]	[illegible]	[illegible]
Johnston et al. 1969	[illegible]	CB	[illegible] for 5 years	[illegible]	[illegible]
[illegible]	[illegible]	CB	[illegible]	[illegible] smoked 29% [illegible]	TR

[b]CB = chronic bronchitis, E = emphysema, B = bronchiectasis, A = asthma.
[c]C = co-trimoxazole, T = tetracycline, OL = olea[illegible], P = penicillin, O = oxytetracycline, SU = sulphonamide, PH = phenethicillin, CH = chloramphenicol, SUL = sulphormethoxine, TR = trimethoprim.

colleagues (1997) conducted a multicenter trial that enrolled patients with COPD, a history of heavy smoking (20 or more pack-years[1]), and airway obstruction (FEV_1 less than 70 percent predicted). There was no difference in the cumulative incidence of acute symptomatic exacerbation between the placebo group and the treatment group (44.5 percent versus 43.7 percent, RR = 1.02 [95 percent CI, 0.81–1.28]). The risk of hospitalization for a respiratory problem was lower in the treatment group (16.2 percent versus 23.2 percent, RR = 0.70 [95 percent CI, 0.46–1.06]). Moreover, the average duration of hospitalization for a respiratory problem was lower in the oral vaccination group (1.5 versus 3.4 days per person). The treatment had no impact on FEV_1 levels, which declined 5.5 mL in the treatment group and 7.5 mL in the placebo group, or on a health-related quality-of-life index (health status questionnaire SF-36 physical and mental component summary scores and eight subscales). Although the evidence is mixed, the oral vaccination trials suggest that bacterial infections play a role in COPD exacerbations and that smoking, as the major cause of COPD, acts on the causal pathway to acute infections.

Antibiotics and Acute Bronchitis. Clinical trials assessing the efficacy of antibiotic treatments for acute bronchitis also indirectly addressed the role of smoking in acute respiratory infections among persons with chronic lung disease (Howie and Clark 1970; Stott and West 1976; Franks and Gleiner 1984; Williamson 1984;

[1]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.

Main outcome measures	Findings (antibiotic vs. placebo)*
• Self-reported subjective improvement	29 vs. 31% (p = NS**)
• Proportion of patients with acute infection	67 vs. 68% (p = NS)
• Proportion [illegible] ralized	33 vs. 4[illegible] (p = NS)
• Proportion with purulent sputum	62 vs. 71[illegible] (p = NS)
• Vital capacity during treatment (mean percent predicted)	99 vs. 64% (p = NS)
• [illegible]	[illegible]
• [illegible]	[illegible]
• [illegible]	[illegible]
• Reduction in proportion [illegible] exacerbations	[illegible]
• Number of exacerbations (mean)	[illegible]
• Days lost from work (mean days per winter)	[illegible]
• Reduction in sputum volume (mL)	[illegible]
• Change in FEV_1 over 3 years (percent predicted)	[illegible]
• Change in mean number of exacerbations	[illegible]
• Change in FEV_1 (mean liters)	0.08 [illegible] (p = NS)

*NS = Not significant.
**All p values given are for between-group comparisons (antibiotic vs. placebo).

Brickfield et al. 1986; Dunlay et al. 1987; Scherl et al. 1987; Hueston 1994; Verhelj et al. 1994; King et al. 1996). Although these clinical trials excluded persons with overt COPD, the prevalence of current smoking among patients was substantial (32 to 55 percent). In three trials, at least 50 percent of patients indicated current smoking (Howie and Clark 1970; Franks and Gleitner 1984; Hueston 1994). Other reviews have established the strong association between current smoking and a decrement in pulmonary function (USDHHS 1990; see "Chronic Respiratory Diseases" later in this chapter). Epidemiologic studies also indicate a higher risk of acute bronchitis in persons with COPD (Monto and Ross 1977, 1978). As a consequence, these clinical trials of acute bronchitis likely included persons with smoking-related airway obstruction.

Taken together, these randomized, double-blind, controlled clinical trials suggest that antibiotic treatments provide a small clinical benefit compared with a placebo (Howie and Clark 1970; Stott and West 1976; Franks and Gleitner 1984; Williamson 1984; Brickfield et al. 1986; Dunlay et al. 1987; Scherl et al. 1987; Hueston 1994; Verhelj et al. 1994; King et al. 1996). A meta-analysis of these clinical trials indicated that antibiotic treatments were associated with a duration of cough and sputum production that was one-half day shorter (Beut et al. 1999). The efficacy of antibiotics supports a causal role of bacterial infections in acute bronchitis.

Of the five clinical trials that used current smoking status to stratify analyses of clinical outcomes (Franks and Gleitner 1984; Brickfield et al. 1986; Dunlay et al. 1987; Verhelj et al. 1994; King et al. 1996), all but one found no evidence of an effect modification from smoking (Brickfield et al. 1986). All of the studies found a similar salutary effect from antibiotics on

the duration of respiratory symptoms in both smokers and nonsmokers (Franks and Gleitner 1984; Brickfield et al. 1986; Dunlay et al. 1987; Verhelj et al. 1994; King et al. 1996). In a randomized, placebo-controlled trial of erythromycin for acute bronchitis involving 50 patients from a family practice clinic, antibiotics appeared to attenuate the duration of coughing and sputum production only among nonsmokers (Brickfield et al. 1986). Although these studies are limited by low power for stratified analysis, the overall evidence suggests no difference in antibiotic efficacy between smokers or nonsmokers.

These findings suggest that the incidence of bacterial infection as a cause of acute bronchitis is similar in smokers and nonsmokers. As a consequence, these studies provide indirect evidence that current smoking does not cause acute bacterial bronchitis in persons who, on average, are likely to have decreased pulmonary function. A major limitation of these studies is the absence of any evaluation of viral respiratory infections.

Evidence Synthesis

Although previous Surgeon General's reports have examined the effects of smoking on acute respiratory infections (USDHHS 1990, 1994), the impact of smoking on persons with a preexisting chronic lung disease was not previously reviewed. The preponderance of evidence presented in this section implicates smoking as a cause of acute respiratory infections among persons with COPD. The Tecumseh study indicated that COPD predisposes smokers to a greater risk of acute respiratory infections, and more recent data confirm that COPD is strongly associated with the development of invasive pneumococcal disease (Nuorti et al. 2000). Although the epidemiologic data are not consistent across studies and study outcomes (i.e., self-reported acute respiratory infection, serologic evidence, pulmonary function decrement, and death from respiratory infection), controlled clinical trials have established the efficacy of antibiotics in treating acute COPD exacerbations. Clinical trials of antibiotics as a prophylaxis against acute infections yielded conflicting results and did not clearly establish efficacy in persons with COPD. The evidence did not clearly establish efficacy in persons with COPD, or whether smoking increases the frequency of acute bacterial bronchitis or modifies the effects of antibiotics in persons with reduced lung function. The oral vaccination trials indicated a reduction in the risk of acute infections. However, none of these studies explicitly evaluated the interaction between COPD and smoking, which would directly address the specific effects of smoking on acute respiratory infections in persons with chronic lung diseases.

Taken together, the epidemiologic and clinical trial evidence indicates that smoking probably acts on the causal pathway to an acute respiratory infection in persons with COPD. However, studies did not clearly separate the risk from remote effects of cigarette smoking (mediated by chronic airway obstruction and its attendant complications) from the immediate effects (through the alteration of immune or inflammatory functions). In vitro and in vivo studies support a biologic basis for the immediate adverse impact of smoking on acute respiratory infections.

The data also support an exposure-response relationship between smoking intensity and the risk of chronic bronchitis (Monto and Ross 1978) and the risk of self-reported acute lower respiratory tract infections among persons with chronic bronchitis (Monto and Ross 1978). For other outcome measures, exposure-response relationships have not been clearly demonstrated (Monto and Ross 1977). One investigation demonstrated an association between smoking intensity and the risk of death from an infection among persons with COPD (Prescott et al. 1995).

The evidence supports the causal role of cigarette smoking in acute asthma exacerbations, and acute respiratory viral infections are an important cause of asthma exacerbations. As a consequence, smoking may precipitate an exacerbation by promoting a viral infection. However, evidence does not directly address this possible mechanism, and further research is needed to clarify the precise impact of smoking on acute asthma.

Conclusions

1. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and acute respiratory infections among persons with preexisting chronic obstructive pulmonary disease.

2. In persons with asthma, the evidence is inadequate to infer the presence or absence of a causal relationship between smoking and acute asthma exacerbation.

Implications

Both COPD and asthma are chronic respiratory conditions associated with substantial morbidity, activity limitation, and economic costs. Although sufficient data exist to infer a causal relationship between

smoking and an increased risk for acute respiratory infections in persons without chronic respiratory diseases, effects in persons with chronic lung diseases are less clearly established. Further research should specifically evaluate the impact of current smoking status on acute respiratory infections among persons with COPD and asthma. Particularly in persons with COPD, the effects of past and current smoking should be evaluated both separately and together. The effects of current and past smoking intensity also should be examined.

Conclusive data confirming the health care costs of smoking-related respiratory infections would place the problem in a larger public health context. Clinical practice guidelines could then incorporate more precise information about the potential benefits of smoking cessation.

Chronic Respiratory Diseases

Chronic respiratory diseases are a heterogeneous group of disorders that affect mainly the conducting airways and alveoli, two main components of the respiratory system. A major function of the airways is to conduct air to the alveoli, also known as the lung parenchyma, where gas exchange occurs. There, oxygen is taken up by red blood cells, and carbon dioxide is removed from the bloodstream. In addition, the airways provide defenses against inhaled particles and other agents that impair the airway walls.

Conclusions of Previous Surgeon General's Reports

Past reports of the Surgeon General on active cigarette smoking and chronic respiratory diseases have emphasized respiratory symptoms, lung function, and COPD. Key conclusions of those reports relevant to the topics are summarized in Table 4.13. Although these topics continue to be important public health concerns and are updated in this review, this report also addresses other chronic respiratory diseases including [illegible] of the airways, such as asthma, and diffuse [illegible] lung diseases, such as pulmonary fibrosis. The rationale for broadening the scope of diseases discussed in this report is based on a growing body of [illegible] associations of cigarette smoking with other [illegible] respiratory diseases. The potential for synergism between cigarette smoking and specific occupational exposures, which was reviewed in the 1964 Surgeon General's report (USDHHS 1985), is not considered in this report.

Because of the extensive literature reviews in previous Surgeon General's reports on chronic respiratory diseases, this section is limited largely to research published between 1989 and January 2000. The search strategy used to identify references in the MEDLINE database included smoking as a major MEDLINE term, or smoking as a descriptor with tobacco or smoking in the title field. These terms were then linked to lung growth and development, lung function, respiratory symptoms, obstructive lung diseases, asthma, and pulmonary fibrosis. In addition, tables of contents were reviewed from two publications, *American Journal of Respiratory and Critical Care Medicine* and *Thorax*, for issues published through April 2000.

The organization of this review follows lung growth and development through developmental periods (i.e., childhood versus adulthood) during which time the various respiratory diseases become clinically apparent. The available evidence suggests that the development of chronic respiratory diseases, particularly chronic airflow obstruction, may result from impaired lung development and growth, a premature onset of declining lung function, an accelerated decline in lung function, or any combination of these conditions (Figure 4.1).

Biologic Basis

Airway development in utero, alveolar proliferation during the first 12 through 24 months of life (Burri 1997), and lung growth to adulthood are critical to the level of mechanical functioning of the lungs. Impaired growth in utero from exposure to maternal smoking may begin a process that predisposes the infant to chronic respiratory diseases in childhood or adulthood. Exposure to secondhand smoke in infancy and childhood, and active smoking during childhood and

Table 4.13 Conclusions from previous Surgeon General's reports concerning smoking as a cause of chronic respiratory diseases

Risk and statement	Surgeon General's report
Childhood	
"Cigarette smoking during childhood and adu[illegible] produces significant health problems among young people, including [illegible] and phlegm production, an increased number and [illegible] of respiratory illnesses, decreased physical fitness, unfavorable lipid profile, and potential retardation in the rate of lung growth and the level of maximum lung function." (p. 9)	1994
[illegible]	1994
Active cigarette smoking by girls with [illegible] women [illegible]	1994
Adulthood	
Chronic Obstructive Pulmonary Disease (COPD)	
"Cigarette smoking is the most important cause of chronic obstructive lung disease in the United States, and increases the risk of developing chronic bronchitis and reduced expiratory airflow. Pipe and cigar smoking also place smokers at increased risk, but it has not been established that this is [illegible]." (p. 3)	1964
Cig[illegible] smoking is the most common cause of COPD. [illegible] disease [illegible] United States [illegible]	1984
"There was a decrease in the age-adjusted death rates for [illegible] from 1968 to 1978 [illegible] Cancer Prevention Study II [illegible] among adults who were current smokers regularly." (p. 2)	1989
"The most powerful [illegible] from [illegible] cigarette smoking." (p. 2)	1989
In 1985, [illegible] COPD deaths. (p. 20)	1989
"Cigarette smoking is a primary cause of COPD in women, and the risk increases with the amount and duration of smoking. Approximately 90 percent of mortality from COPD among women in the United States can be attributed to cigarette smoking." (p. 14)	2001

Table 4.13 Continued

Risk and statement	Surgeon General's report
Adulthood	
"Mortality rates for COPD have increased among women over the past 20 to 30 years." (p. 141)	2001
Occupational Lung Diseases	
"[T]here is evidence that smokers who are exposed to asbestos have a greatly increased risk of developing lung cancer and other diseases." (p. 15)	1979
"In those with chronic exposure to asbestos, disease and exposure to smoking combine multiplicatively to produce a risk of lung cancer that is substantially greater than the sum of the risks from the two agents separately." (p. 21)	1979
Asbestos	
"Smoking and asbestos exposure appear to have an interactive effect on [the] development of lung cancer. Cessation of smoking has been shown to reduce the risk of lung cancer in asbestos workers, although the risk remains higher than that for nonsmoking asbestos workers." (p. 21)	1979
"Lung cancer mortality and chest roentgenographic abnormalities were more frequent in asbestos workers who smoked cigarettes than in those who did not smoke. Cigarette smoking appears to act synergistically with asbestos exposure to increase the risk of lung cancer. Cessation of smoking by asbestos workers appears to reduce the risk of lung cancer, although the risk remains higher than that for persons who have never smoked." (p. 21)	1979
"Asbestos exposure, with or without clinical evidence of asbestosis, can produce small but significant decrements in lung function. Cigarette smoking has also been shown to produce small but significant decrements in lung function. Asbestos workers who smoke cigarettes have been found to have greater decrements in lung function than workers who do not smoke cigarettes. Cessation of smoking by asbestos workers appears to reduce the risk of lung cancer, although the risk remains higher than that for persons who have never smoked." (p. 21)	1979
"Asbestos exposure, with or without clinical evidence of asbestosis, can produce small but significant decrements in lung function. Cigarette smoking has also been shown to produce small but significant decrements in lung function. Asbestos workers who smoke cigarettes have been found to have greater decrements in lung function than workers who do not smoke cigarettes. Cessation of smoking by asbestos workers appears to reduce the risk of lung cancer, although the risk remains higher than that for persons who have never smoked." (p. 21)	1982
"Asbestos exposure is the most important occupational risk factor for lung cancer in the United States. Cigarette smoking is the most important risk factor for lung cancer in the general population. Asbestos workers who smoke have a greatly increased risk of lung cancer. Cessation of smoking by asbestos workers appears to reduce the risk of lung cancer, although the risk remains higher than that for persons who have never smoked." (p. 14)	1985
"Asbestos exposure, with or without clinical evidence of asbestosis, can produce small but significant decrements in lung function. Cigarette smoking has also been shown to produce small but significant decrements in lung function. Asbestos workers who smoke cigarettes have been found to have greater decrements in lung function than workers who do not smoke cigarettes. Cessation of smoking by asbestos workers appears to reduce the risk of lung cancer, although the risk remains higher than that for persons who have never smoked." (p. 14)	1986
"Asbestos exposure is the most important occupational risk factor for lung cancer in the United States. Cigarette smoking is the most important risk factor for lung cancer in the general population. Asbestos workers who smoke have a greatly increased risk of lung cancer. Cessation of smoking by asbestos workers appears to reduce the risk of lung cancer, although the risk remains higher than that for persons who have never smoked." (p. 14)	1989
Silica	
"Silicosis, acute silicosis, mixed dust silicosis, silicotuberculosis, and diatomaceous earth pneumoconiosis are causally related to silica exposure as a sole or principal etiological agent." (p. 15)	1985

Table 4.13 Continued

Risk and statement	Surgeon General's report
Adulthood	
"Epidemiological evidence, based on both cross-sectional and prospective studies, demonstrates that silica dust is associated with chronic bronchitis and chronic airways obstruction. Silica dust and smoking are major risk factors and appear to be additive in producing chronic bronchitis and chronic airways obstruction. Most studies indicate that the smoking effect is stronger than the silica dust effect." (p. 15)	1985
"Further epidemiological evidence is required to clarify the exposure-response relationship between silica dust and the development of chronic airways obstruction caused by cigarette smoking." (p. 15)	1985
"Coal dust exposure is clearly the major etiologic factor in the production of the radiologic changes of coal workers' pneumoconiosis (CWP). Cigarette smoking markedly increases the prevalence of irregular opacities on the chest roentgenograms of smoking coal miners, but appears to have little effect on the prevalence of small rounded opacities or complicated CWP." (p. 13)	1985
"The smoking category of simple radiologic CWP is [illegible] chronic cough and phlegm production, chronic expiratory airflow limitation, and premature death from both chronic and nonchronic [illegible]." (p. 14)	1985
"Simple coal [illegible] are not [illegible] coal [illegible] significant [illegible] among [illegible]." (p. 14)	1985
"Cigarette smoking and duration of coal dust exposure appear to be independent factors and [illegible] in the prevalence of [illegible] bronchitis." (p. 14)	1985
"Interaction between exposure to coal dust and cigarette smoking in the development of known chronic obstructive lung disease [illegible] to exert a greater than additive effect [illegible]." (p. 14)	1985
"[T]he levels of coal dust exposure that are likely to result in [illegible] severe complicated CWP. However, the airway abnormalities in coal miners and the [illegible] reduction in [illegible] of chronic smoking underline the importance of [illegible] dust exposure in [illegible] chronic airways obstruction." (p. 14)	1985

Table 4.13 Continued

Risk and statement	Surgeon General's report
Smoking cessation	
"Smoking cessation reduces rates of respiratory symptoms such as cough, sputum production, and wheezing, and respiratory infections such as bronchitis and pneumonia, compared with continued smoking." (p. 11)	1990
"For persons without chronic obstructive pulmonary disease (COPD), smoking cessation improves pulmonary function to a level within a few years of the cessation." (p. 11)	1990
"Cigarette smoking is the single most important risk factor for COPD. The risk of developing COPD increases with the number of cigarettes smoked per day and the number of years of smoking. Cessation of smoking results in a return of the rate of decline in FEV$_1$ to that of nonsmokers." (p. 11)	1990
"While cessation of smoking in the COPD patient will not restore lung function to normal, it will substantially reduce the rate of decline in lung function." (p. 11)	1990
"The rate of decline in lung function is slower among women who stop smoking than among women who continue to smoke." (p. 14)	1979

Sources: U.S. Department of Health, Education, and Welfare 1964; U.S. Department of Health and Human Services 1984, 1985, 1989a, 1990, 1994, 2001.

adolescence, further contribute to impaired lung growth and the risk of developing respiratory diseases (Fletcher et al. 1976; Samet et al. 1983; USDHHS 1984; Tager et al. 1988; Sherrill et al. 1991; Helms 1994; Samet and Lange 1996). Active smoking in adulthood leads to an accelerated decline of FEV in some smokers and ultimately to the development of clinically apparent COPD (USDHHS 1984).

Lung Development In Utero

Epidemiologic Evidence

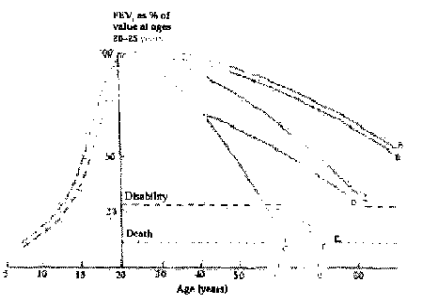
Although measuring lung function during infancy to detect in utero effects presents many challenges and is an evolving technique, during the past decade our knowledge about the effects of maternal smoking during pregnancy has grown (Dezateux and Stocks 1997; Morgan and Martinez 1998). Studies have consistently documented evidence of impaired lung function in early infancy following in utero exposure to maternal smoking (Table 4.14) (Young et al. 1991; Hanrahan et al. 1992; Tager et al. 1995; Stick et al. 1996; Lodrup Carlsen et al. 1997; Hoo et al. 1998; Dezateux et al. 1999; Milner et al. 1999). A number of measures of ventilatory function have been used, including (1) measures of expiratory flow: maximal flow at functional residual capacity ($\dot{V}_{maxFRC}$) and the ratio of time to peak tidal expiratory flow to expiratory time (tPTEF/tE); (2) airway resistance and respiratory system conductance; and (3) respiratory system compliance. In addition, bronchial responsiveness to pharmacologic agents has been measured in a smaller number of studies (Young et al. 1991; Clarke et al. 1995).

To determine the effects of in utero exposures to maternal smoking, separate from later exposures to secondhand smoke and lower respiratory tract infections, pulmonary function tests have been performed in healthy infants soon after birth and even before hospital discharge (Stick et al. 1996; Lodrup Carlsen et al. 1997; Hoo et al. 1998; Milner et al. 1999). Three studies that looked at examinations conducted before hospital discharge identified decrements in tPTEF/tE in relation to maternal smoking during pregnancy (Stick et al. 1996; Lodrup Carlsen et al. 1997; Hoo et al. 1998). Instead of using a measure of airflow, Milner and colleagues (1999) measured respiratory system conductance and respiratory system compliance and found decrements in these parameters that differed between male and female infants (Table 4.14). An inverse dose-response relationship between the number of cigarettes smoked per day during pregnancy and the level of pulmonary function was found in two of the investigations (Stick et al. 1996; Lodrup Carlsen et al. 1997).

Further evidence for an adverse effect from maternal smoking during pregnancy has been found in infants who had pulmonary function measurements later in infancy but before having any LRI (Young et al. 1991; Hanrahan et al. 1992; Tager et al. 1995; Dezateux et al. 1999). Young and colleagues (1991) measured pulmonary function and airway hyperresponsiveness to histamine in 63 healthy infants from a prenatal clinic in Perth, Australia. The infants were categorized into four groups on the basis of a family history of asthma and parental cigarette smoking during pregnancy, but prenatal and postnatal exposures to cigarette smoke could not be separated. At a mean age of 4.5 weeks, rates of forced expiratory flow (FEF) did not differ among the four groups. However, airway responsiveness was greater in infants whose parents had smoked during pregnancy.

An increased risk of lower respiratory tract illnesses, including wheezing, and subsequent reductions in expiratory airflow and airway hyperresponsiveness during infancy may be consequences of maternal smoking during pregnancy (Martinez et al. 1988; Stick et al. 1991; Tager et al. 1993; Clarke et al. 1995; Dezateux et al. 1999). Martinez and colleagues (1988) measured pulmonary function in 124 infants from Tucson, Arizona, before any lower respiratory

Figure 4.3 Theoretical curves depicting varying rates of decline of forced expiratory volume in one second (FEV_1)



Note: Curves A and B represent never smokers and smokers, respectively, declining at normal rates. Curve C shows increased declines without the development of chronic obstructive pulmonary disease (COPD). Rates of decline for former smokers are represented by curves D and E for those without and with clinical COPD, respectively. Curves F and G show rates of decline with continued smoking after developing COPD.
Sources: Speizer and Tager (1979); U.S. Department of Health and Human Services 1990, p. 281.

1998). Instead of using a measure of airflow, Milner and colleagues (1999) measured respiratory system conductance and respiratory system compliance and found decrements in these parameters that differed between male and female infants (Table 4.14). An inverse dose-response relationship between the number of cigarettes smoked per day during pregnancy and the level of pulmonary function was found in two of the investigations (Stick et al. 1996; Lodrup Carlsen et al. 1997).

Further evidence for an adverse effect from maternal smoking during pregnancy has been found in infants who had pulmonary function measurements later in infancy but before having any LRI (Young et al. 1991; Hanrahan et al. 1992; Tager et al. 1995; Dezateux et al. 1999). Young and colleagues (1991) measured pulmonary function and airway hyperresponsiveness to histamine in 63 healthy infants from a prenatal clinic in Perth, Australia. The infants were categorized into four groups on the basis of a family history of asthma and parental cigarette smoking during pregnancy, but prenatal and postnatal exposures to cigarette smoke could not be separated. At a mean age of 4.5 weeks, rates of forced expiratory flow (FEF) did not differ among the four groups. However, airway responsiveness was greater in infants whose parents had smoked during pregnancy.

An increased risk of lower respiratory tract illnesses, including wheezing, and subsequent reductions in expiratory airflow and airway hyperresponsiveness during infancy may be consequences of maternal smoking during pregnancy (Martinez et al. 1988; Stick et al. 1991; Tager et al. 1993; Clarke et al. 1995; Dezateux et al. 1999). Martinez and colleagues (1988) measured pulmonary function in 124 infants from Tucson, Arizona, before any lower respiratory

tract illness had occurred, and found that infants whose total respiratory conductance was in the lowest third of the group had an increased risk of a subsequent wheezing illness (OR = 3.7 [95 percent CI, 0.9–15.5]). In a sample of 97 infants from the East Boston, Massachusetts, Neighborhood Health Center, Tager and colleagues (1983) found an association between maternal smoking during pregnancy and an elevated risk for lower respiratory tract illnesses (OR = 1.47 [95 percent CI, 1.08–1.99]). Clarke and colleagues (1985) conducted pulmonary function studies on 79 healthy infants approximately one month of age and followed them during their first year of life. Lower expiratory airflow was associated with a wheezing illness in boys but not in girls, and bronchial hyperreactivity was associated with a wheezing illness in girls but not boys. Dezateux and colleagues (1999) found a significantly higher expiratory airway resistance before there was any evidence of a lower respiratory tract illness in 28 infants who had developed at least one subsequent wheezing illness by one year of age or less, compared with 73 infants who did not have a wheezing illness.

The decrement in pulmonary function associated with in utero exposure to tobacco smoke that is detectable at birth and throughout infancy may persist across childhood and into adulthood. In a cross-sectional survey, Cunningham and colleagues (1994) measured pulmonary function in 8,863 children aged 8 through 12 years from 22 North American communities. In multivariate analyses the children whose mothers reported smoking during pregnancy had significantly lower FEF$_{25}$ and reductions in FEV$_{0.5}$ and FEV$_1$/FVC, compared with the children of mothers who did not smoke during pregnancy. After adjusting for maternal smoking during pregnancy, current maternal smoking was not associated with a significant decrement in lung function. Gilliland and colleagues (2000) examined the relationship between maternal smoking and pulmonary function among 3,357 school children (grades 4, 7, and 10) living in 12 southern California communities. After adjusting for secondhand smoke exposure and other potential confounders, maternal smoking during pregnancy was associated with significant decrements in peak expiratory flows, maximum midexpiratory flows, and FEFs at 75 percent of FVC, but not in FEV$_1$ levels.

Evidence Synthesis

These findings consistently show the effects of maternal smoking during pregnancy, including impaired pulmonary function and lower respiratory tract illnesses during infancy and childhood. Evidence for a causal role of maternal smoking is further strengthened by the dose-response relationship between maternal smoking during pregnancy and the magnitude of decrements in pulmonary function (Stick et al. 1996; Ladrup Carlsen et al. 1997). Because these studies have been restricted to healthy full-term infants, it is unlikely that the findings are a result of other factors that may adversely affect in utero development including poor maternal nutrition, alcohol use, or the intake of other potentially toxic agents.

In utero exposure to maternal smoking may be associated with lower respiratory tract illnesses in childhood, and the subsequent risk for chronic respiratory diseases in adulthood through its effect on birth weights. Lower birth weight has been associated with reduced lung function in childhood. Data on the relationship between birth weight and adult lung function also provide similar indirect evidence (Chan et al. 1989; Barker et al. 1991; Rona et al. 1993). Maternal smoking during pregnancy has been associated with decreased birth weights [see Chapter 5, "Reproductive Effects"], and several studies indicate that birth weight is directly related to the level of expiratory airflow during childhood (Chan et al. 1989; Rona et al. 1993) and adulthood (Barker et al. 1991). Furthermore, self-reports of childhood lower respiratory tract illnesses are associated with chronic airflow obstruction in adulthood (Berglund et al. 1999).

Conclusions

1. The evidence is sufficient to infer a causal relationship between maternal smoking during pregnancy and a reduction of lung function in infants.

2. The evidence is suggestive but not sufficient to infer a causal relationship between maternal smoking during pregnancy and an increase in the frequency of lower respiratory tract illnesses during infancy.

3. The evidence is suggestive but not sufficient to infer a causal relationship between maternal smoking during pregnancy and an increased risk for impaired lung function in childhood and adulthood.

Implication

Although the biologic basis for impaired infant lung function from maternal smoking during pregnancy is not yet fully understood, the causal link provides yet another strong rationale for smoking cessation during pregnancy.

Table 4.14 Studies on the association between maternal smoking during pregnancy and infant lung function

Study	Population	Age at measurement
Young et al. 1991	53 full-term infants with no perinatal problems, major congenital problems, or lower respiratory infections Perth, Australia	Mean, 4.6 weeks; range, 2–10 weeks
Hanrahan et al. 1992	80 healthy infants East Boston, Massachusetts	Mean, 4 weeks; range, 1–8 weeks
Tager et al. 1983	175 healthy infants Berkeley, California	2 months 4 months 9–24 months 3–4 years
Stick et al. 1996	550 healthy infants Perth, Australia	Median, 28 hours after birth; range, 2–96 hours
Dezateux et al. 1999	76 healthy infants Oxford, England	Mean, 2.7 days
Hoo et al. 1998	205 preterm infants (gestational age 32.7 weeks) discharged on oxygen and matched with 60 full-term infants London, United Kingdom	Before hospital discharge
Duval et al. 1985	51 full-term infants with respiratory symptoms in the first month of life and 51 healthy control infants Toronto, Ontario, Canada	Mean, 2.3 weeks (range, 1.7–12.6) for infants tested for lower respiratory symptoms
McEniery et al. 1996	28 full-term, healthy infants London, United Kingdom	Within 72 hours of delivery

[illegible] = forced expiratory volume in 1 second.
tPTEF:[illegible] = time to peak tidal expiratory flow as a proportion of expiratory time

Findings

- Maximal flow at functional residual capacity (V_{max}FRC) percent predicted values were not associated with maternal smoking during pregnancy
- Airway responsiveness to histamine increased significantly with maternal smoking during pregnancy and with a family history of asthma

Maternal smoking	VFT [illegible] (ml/sec)	FEF$_{25-75}$ (ml/sec)
Nonsmokers (n = 70)	150 (-5.5)	92.8 (-1.2)
Continuous smokers (n = 21)	74.3 (-15.9)	41.4 (-5.5)
Variable smokers (n = 10)	131.1 (-28.3)	41.6 (-2.5)

- For infants 12 months of age, maternal smoking during pregnancy was associated with a 19% reduction in VPEFC in girls and a 5% reduction in boys
- Secondhand smoke exposures in the neonatal period was not significant[illegible] associated with decreased pulmonary function

Maternal smoking	n	[illegible] (percent predicted)
1–10 cigarettes/day	[illegible]	2.0 (0.1)
>10 cigarettes/day	[illegible]	2.0 (0.08)

Other factors in [illegible] were associated with decrements in tPTEF. From clinically observed asthma and [illegible]

- In a multivariate regression [illegible] was associated with a 0.[illegible] increase in log(resistance)
- In a multivariate regression [illegible] was associated with a [illegible] (H_2O (95% CI, 0.15 [illegible]

	Maternal smoking	No maternal smoking
V_{max}FRC (mL/sec)	85.2	94.6
tPTEF/tE	0.37	0.40

	Maternal smoking	No maternal smoking
Expiratory raw (airway resistance)	5.20	4.1
Airway resistance (increase in maximum pressure/flow)	0.32	0.34

The odds ratio (OR) of wheezing in the first year of life was associated with maternal smoking during pregnancy: OR = 4.9 (95% CI, 1.8–15.0)

- No reduction in expiratory flow was associated with maternal smoking
- There was reduced respiratory system compliance in boys whose mothers smoked
- There was reduced respiratory system conductance in girls whose mothers smoked

Pathogenesis of Smoking-Induced Lung Injury

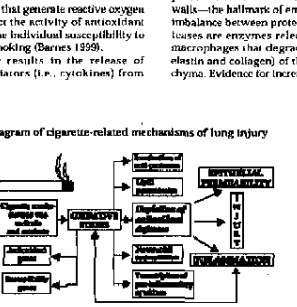
Epidemiologic Evidence

The rate of expiratory airflow depends on elastic recoil forces of the alveoli and on the diameter of the small airways. Complex interactions between smoking-caused changes in the structure and function of small airways and lung parenchyma result in the physiologic finding of chronic airflow limitation (Wright 1992; Thurlbeck 1994). The literature relevant to understanding the mechanisms of smoking-induced COPD has grown substantially in recent years, and points to a complex interplay among a number of biologic processes including oxidative stress, inflammation, protease-antiprotease imbalances, repair processes, and the genetic variations that control these processes (Figure 4.2) (Sandford et al. 1997; Barnes 1998; MacNee and Rahman 1999). The inhalation of cigarette smoke exposes the lungs to high concentrations of oxidant agents and free radicals, which decrease the antioxidant capacity that normally protects epithelial cells from oxidant injury (Repine et al. 1997; Rahman and MacNee 1998). Moreover, several enzymes found in the lungs generate reactive oxygen molecules that may contribute further to the oxidative stress in the lungs. Genetic variations that alter the function of enzymes that generate reactive oxygen molecules, or that affect the activity of antioxidant enzymes, may determine individual susceptibility to COPD from cigarette smoking (Barnes 1999).

Epithelial injury results in the release of proinflammatory mediators (i.e., cytokines) from epithelial cells and inflammatory cells in the airway walls (i.e., lymphocytes and macrophages). These mediators lead to an influx of neutrophils, which also release mediators that perpetuate the cycle of injury and inflammation (Figure 4.2) (MacNee and Rahman 1999; Mills et al. 1999). The inflammatory process is found in the central airways, peripheral airways, and lung parenchyma, even in smokers with normal lung function (Saetta 1999; Saetta et al. 2001). Although an inflammatory process in the small airways (respiratory bronchiolitis) appears to develop in all cigarette smokers, in susceptible smokers the injury progresses and leads to a narrowing of these airways (Botvken et al. 1990; USDHHS 1990; Aguayo 1994). Available evidence suggests that changes in the structure and function of small airways (bronchioles) are fundamental to the development of smoking-induced COPD (Wright 1992; Thurlbeck 1994). Genetic variations that alter the function of several inflammatory mediators, and thus the type of inflammatory response, probably contribute in part to susceptibility to COPD (Barnes 1999). For example, smokers with COPD have a predominance of CD8-positive T lymphocytes in the central and peripheral airways compared with smokers without COPD (O'Shaughnessy et al. 1997; Saetta et al. 1998, 2001).

The inflammatory process may extend into the peribronchiolar alveoli and destroy the alveolar walls—the hallmark of emphysema—when there is an imbalance between proteases and antiproteases. Proteases are enzymes released from neutrophils and macrophages that degrade structural proteins (e.g., elastin and collagen) of the airways and lung parenchyma. Evidence for increased elastin degradation was

Figure 4.2 Summary diagram of cigarette-related mechanisms of lung injury



Source: MacNee and Rahman 1999, p. 583. Reprinted with permission.

reported by Gottlieb and colleagues (1996), who found increased urine desmosine (a by-product of elastin degradation) in smokers who had rapid declines in lung function. Antiproteases released from macrophages and the liver provide a natural defense against proteases. A deficiency in alpha$_1$-antitrypsin, an antiprotease, is a rare genetic variation that causes emphysema, but it is found only in 1 to 2 percent of patients with COPD.

Evidence Synthesis

To date, except for an alpha$_1$-antitrypsin deficiency, the role of genetic variations in the development of COPD has received limited attention (Sandford et al. 1997; Barnes 1999; Takizawa et al. 2001). Family studies have demonstrated a genetic influence on the level of FEV_1, and segregation analysis has provided evidence that the effect is polygenic. Moreover, in case-control studies of COPD patients, a family history of COPD has proven to be a risk factor for COPD. Candidate genes for susceptibility to cigarette smoke and COPD that are under active investigation include the numerous genes that control peripheral airway inflammation, oxidant levels, and the protease-antiprotease balance (Higham et al. 2000; Sakao et al. 2001; Sandford et al. 2001).

Conclusion

1. Active smoking causes injurious biologic processes (i.e., oxidant stress, inflammation, and a protease-antiprotease imbalance) that result in airway and alveolar injury. This injury, if sustained, ultimately leads to the development of chronic obstructive pulmonary disease.

Implication

Although smoking prevention and cessation remain the cornerstones for preventing smoking-induced chronic respiratory diseases (USDHHS 1990), further research on the biologic mechanisms of airway and alveolar injury caused by smoking may provide new approaches for preventing smoking-induced lung diseases among smokers unable to quit.

Growth of Lung Function in Infancy and Childhood

Epidemiologic Evidence

In addition to the adverse effects on pulmonary function of in utero exposure to maternal smoking and parental exposure to parental smoking (National Research Council 1986; USDHHS 1986; U.S. Environmental Protection Agency 1992), active cigarette smoking during childhood and adolescence has the potential for retarding the rate of lung growth and the level of maximum lung function (Table 4.13) (USDHHS 1994), thus increasing the risk for COPD in adulthood (Figure 4.1). Results from six cohort studies of lung function in children and adolescents published from 1982–1992 were reviewed in the 1994 Surgeon General's report (USDHHS 1994). Two representative publications from that report (Tager et al. 1985, 1988) are summarized here along with two investigations that were not reviewed in the 1994 report (Sherrill et al. 1991; Gold et al. 1996).

In a longitudinal study of 669 children and adolescents aged 5 through 19 years in East Boston, Massachusetts, Tager and colleagues (1985) found that among adolescents who started to smoke at 15 years of age and continued to smoke, the percent predicted FEV_1 level at 20 years of age was only 92 percent of the expected FEV_1 level for nonsmokers. Subsequently, Tager and colleagues (1988) analyzed spirometric measurements from at least one FVC test performed during 1975–1985 in each of 974 females and 913 males aged 5 years and older. For girls, a linear increase in FEV_1 levels ended approximately one year earlier for current smokers (at 17 years of age) than for nonsmokers without respiratory symptoms (at 18 years of age); the average maximal FEV_1 values were 2.9 L and 3.1 L, respectively. For nonsmokers with respiratory symptoms, the estimated maximal FEV_1 level was identical to that for current smokers (2.8 L). For boys, the estimated maximal FEV_1 level was identical for asymptomatic nonsmokers (those who did not have a diagnosis of chronic bronchitis or emphysema, or evidence of chronic respiratory symptoms), symptomatic nonsmokers, and current smokers (4.9 L); but was attained at a much earlier age for current smokers (at 18 through 19 years of age) compared with asymptomatic nonsmokers (aged 20 through 24 years) and symptomatic nonsmokers (21 years). Sherrill and colleagues (1991) assessed growth curves in smokers classified as asymptomatic. They found that among women, cessation of lung function growth occurred at 22 years of age in asymptomatic smokers and at 23 years of age in asymptomatic women who had never smoked. Among female smokers with respiratory symptoms, lung function growth ended at 21 years of age, three years earlier than for those who had never smoked. Among asymptomatic men, the authors found no differences in the age of lung growth cessation between nonsmokers and smokers (23 years of age). Among

symptomatic male smokers, however, lung growth cessation occurred at a younger age (25 years of age) *compared with symptomatic nonsmokers (27 years* of age).

In a cohort of 4,992 girls and 5,158 boys from 10 to 18 years of age tested annually with spirometry, Gold and colleagues (1996) examined the effects of cigarette smoking on the rate of lung function growth and the level of lung function attained. Among girls smoking five or more cigarettes per day, the rate of increase in FEV_1 levels was slower by 31 mL/year (95 percent CI, 18.0–48.0 mL/year) than among girls who had never smoked. At 17 to 18 years of age, FEV_1 levels began to decline among girls who smoked while staying at a plateau among girls who did not smoke. Although smoking five or more cigarettes per day slowed the rate of increase in FEV_1 levels in boys, the magnitude of the effect (slower by 9 mL/year; 95 percent CI, -6.0 to 24.0 mL/year) was less than that in girls. There was an inverse association between the amount smoked and the level of FEV_1/FVC and FEF between 25 and 75 percent of the FVC ($FEF_{25-75\%}$). The number of cigarettes smoked was not associated with FVC or FEV_1 levels.

Evidence Synthesis

There have been only a limited number of longitudinal investigations of active smoking during childhood and adolescence because of the complex logistics of such studies. However, the findings are consistent for various populations. In smokers, lung function growth is slower during childhood and adolescence, prematurely ceases, and begins to decline in late adolescence and early adulthood. The evidence suggests a causal role for active smoking. This causal link is strengthened by the finding of a dose-response relationship between smoking and the level of FEV_1/FVC and between smoking and $FEF_{25-75\%}$. Additionally, the inflammatory process caused by smoking would be initiated at any age, and the lungs of young smokers show evidence of airways inflammation and injury.

Conclusions

1. The evidence is sufficient to infer a causal relationship between active smoking and impaired lung growth during childhood and adolescence.

2. The evidence is sufficient to infer a causal relationship between active smoking and the early onset of lung function decline during late adolescence and early adulthood.

Implications

These conclusions provide a strong rationale for interventions to prevent children and adolescents from starting to smoke and for helping young smokers to quit. Future studies should determine the effects of smoking cessation on the rate of lung growth, and they should follow smokers from adolescence into their fourth and fifth decades of life when COPD is first diagnosed. Addressing these gaps in knowledge could provide further evidence of a causal link between active smoking during childhood and the risk for later development of COPD.

Decline of Lung Function

Epidemiologic Evidence

Results from longitudinal investigations of adults between their second and third decades—the period of transition from lung growth to a plateau of variable length and then to decline—suggest that cigarette smoking causes a premature onset of lung function decline and, to a lesser extent, a more rapid decline (Tager et al. 1988; Sherrill et al. 1991). In the East Boston study, estimates of the age range when lung function begins to decline were wide but tended to be earlier for current smokers compared with asymptomatic or symptomatic nonsmokers (Tager et al. 1988). After *the period of maximal lung growth, there is a pro*longed plateau period for the FEV_1 level in nonsmoking men before the FEV_1 declines (late in the fourth decade of life). This decline is estimated to begin 10 years earlier (i.e., late in the third decade of life) in asymptomatic nonsmokers and 15 years earlier in current smokers (i.e., in the middle of the third decade). Among all women, the onset of decline begins at an earlier age compared with that of men, and female current smokers had a more rapid earlier decline (-20 mL/year) and an earlier age of onset of a more rapid decline compared with nonsmoking women. In the population-based study of respiratory diseases in Tucson, Arizona, Sherrill and colleagues (1991) also found that symptom status modified the rate of decline. The rate of decline was similar for asymptomatic male smokers and nonsmokers until approximately 48 years of age, when the average rate of decline for smokers increased from -29 mL/year to -48 mL/year. Among symptomatic smokers, the increased rate of decline occurred at a younger age (34 years of age). The FEV_1 level was lower for symptomatic female smokers beginning in the late teenage years, but there

was little difference in the subsequent rate of FEV_1 decline between smokers and nonsmokers.

In cross-sectional and cohort studies of ventilatory function, a higher average rate of FEV_1 decline has been consistently found in current cigarette smokers compared with former smokers and nonsmokers (Fletcher et al. 1976; Kauffmann et al. 1989; USDHHS 1984, 1990). In cohort studies [illegible] age rate of FEV_1 decline among nonsmokers [illegible] from 17 to 61 mL/year, and the decline among smokers [illegible] ded the decline among nonsmokers by 7 to 27 mL/year (USDHHS 1990). Furthermore, while the rate of [illegible] decline for smokers and nonsmokers is highly variable, the distribution of FEV_1 decline rates is shifted toward a higher proportion of sustained smokers with rapid rates of decline. As the amount of cigarette smoking increases, the rate of decline increases (Xu et al. 1992, 1994; Burchfiel et al. 1996; Vestbo et al. 1996; Beleusova et al. 1997; Scanlon et al. 2000; Vollmer et al. 2000). For some smokers, the increased rate of decline eventually results in a FEV_1 level associated with dyspnea and a limitation of activities at this level, the clinical diagnosis of COPD is usually made (Figure 4.1).

Because not all smokers develop COPD, research is increasingly directed at identifying factors that may heighten susceptibility to rapid rates of FEV_1 decline. Factors that have been examined include gender (Xu et al. 1994; Scanlon et al. 2000; Vollmer et al. 2000), race and ethnicity (Scanlon et al. 2000; Vollmer et al. 2000), alcohol use (Burchfiel et al. 1998), diet and use of nutritional supplements (Carey et al. 1998), anthropometric characteristics (Burchfiel et al. 1998), respiratory symptoms (Jaakkola et al. 1991a,b; Sherman et al. 1992; Burchfiel et al. 1996; Scanlon et al. 2000), FEV_1 levels (Burrows et al. 1987; Scanlon et al. 2000), airways hyperresponsiveness (Frew et al. 1992, Tashkin et al. 1996), comorbid conditions such as asthma and *coronary heart disease (Burchfiel et al. 1996; Lange* et al. 1998), and occupational and environmental exposures (Xu and Wang 1998). Investigations of these factors are ongoing and firm conclusions cannot yet be reached on their roles in modifying the risk for COPD in smokers.

Available investigations provide conflicting results about the relative rates of FEV_1 decline among women who smoke compared with men who smoke (Xu et al. 1994; Scanlon et al. 2000; Vollmer et al. 2000). Xu and colleagues (1994) suggested that women may have a higher rate of FEV_1 decline. They hypothesized that different distributions of unhealthy participants by gender in nonsmoking reference groups may explain conflicting results in studies that compared rates of FEV_1 decline in women and men. Other factors that may modify the effects of smoking and contribute to gender differences in study findings include the year of birth of study participants (birth cohort) and the time period of a study (Samet and Lange 1996). In a study from the Netherlands, Xu and colleagues (1995) reported a significant interaction between age and birth cohorts in relation to declines in FEV_1 levels in women but not in men. The modifying effects of a birth cohort may partially reflect changes in smoking behavior and perhaps in the products smoked.

Several studies have shown that women have a higher prevalence and degree of bronchial hyperreactivity (Leynaert et al. 1997), associated with an accelerated rate of decline in FEV_1 levels, compared with men (Tashkin et al. 1996; Scanlon et al. 2000). This gender difference in bronchial hyperreactivity may contribute to a higher risk in women for developing COPD. Scanlon and colleagues (2000) found in the Lung Health Study that women who continued to smoke over a five-year period had a greater annual decline in FEV_1 levels than did men with comparable levels of smoking (-1.08 percent predicted and -0.77 percent predicted, respectively), but the statistical significance of the difference was not reported. The increased rate of decline among women was associated with a greater degree of bronchial hyperreactivity.

Biologic differences between women and men, including differences in lung mechanics and hormonal factors, may affect susceptibility to the adverse effects of cigarette smoke, but limited data are available to test these hypotheses. Whether there are gender differences from the effects of smoking on changes in lung function remains unclear.

Scant data are available on racial and ethnic differences in the rates of FEV_1 decline (Scanlon et al. 2000; Vollmer et al. 2000). In the Lung Health Study, Vollmer and colleagues (2000) combined spirometric data from eight population-based observational studies or clinical trials conducted in North America to examine the relationship between smoking, lung function, race, and ethnicity. Overall, this cross-sectional analysis included 23,812 men (66 percent white, 14 percent black, 4 percent Hispanic, 12 percent Asian/Pacific Islander, and 3 percent American Indian) and 16,921 women (62 percent white, 25 percent black, 8 percent Hispanic, and 7 percent American Indian). The estimated average excess FEV_1 decline attributed to smoking was highest among whites (-6 mL/pack-year) and similar in the other racial and ethnic groups (-3 to -4 mL/pack-year). However, the greatest differences among racial and ethnic groups were limited to the heaviest

Table 4.15 Studies on the association between smoking and rates of forced expiratory volume in one second (FEV_1) decline

Study	Population	Period of study/follow-up
Jaakkola et al. 1991a	214 white women 177 white men Aged 15–40 years at baseline Montreal, Canada	Baseline: 1980–1981 Follow-up: 1988–1989
[illegible] et al. 1991b	678 women [illegible] Aged 15–40 years Montreal, Canada	1985
Frew et al. 1992	[illegible]	[illegible]
[illegible] et al. 1992	[illegible]	[illegible]
[illegible] et al. 1996	[illegible]	[illegible]
Sandford et al. 1996	1,981 men Aged 40–69 years	Baseline: 1975 Follow-up: 1991–1993
Burchfiel et al. 1996	4,821 Japanese-American men Aged 45–68 years Honolulu, Hawaii	Baseline: 1968 Follow-up: 1971–1975
[illegible] et al. 1997	560 women 530 men Aged 19–73 years Amsterdam	1991–1994

*Pack-years = [illegible] of smoking multiplied by [illegible] of packs of cigarettes smoked per day.

Rate of FEV_1 decline	Type of study/comments
-0.42 mL/year/cigarette/day	Longitudinal; participation was 38% at follow-up
-0.35 mL/year/cigarette/day	Cross-sectional; significant interaction between smoking and occupational exposures
Current smokers: -23.8 mL/year Former smokers: -21.0 mL/year Never smokers: -23.8 mL/year	Longitudinal; beneficial effect of quitting was seen over the first 4 years of follow-up; no clear difference in current or never smokers
Women Continuing smokers: -44.0 mL/year Former smokers: -30.1 mL/year Never smokers: -26.6 mL/year Men Continuing smokers: -44.0 mL/year Former smokers: -37.7 mL/year Never smokers: -31.7 mL/year	Longitudinal; respiratory symptoms were associated with a more rapid decline
-4.0 mL/year/cigarette/day	Cross-sectional
Smokers: -64 mL/year Nonsmokers: -45 mL/year	Longitudinal
Continuous smokers: -34 mL/year Never smokers: -22 mL/year	Longitudinal; rapid FEV$_1$ decline was independently associated with pack-years of smoking, and reduced subscapular skinfold

FEV_1 decline (mL/year)	% current smokers
<30	40.0
30–59	50.5
≥60	59.9

-2.0 mL/cigarettes/day	Cross-sectional

Table 4.15 Continued

Study	Population			Period of study/follow-up
Xu and Wang 1998	Beijing, China 1,061 men Aged 40–69 years Beijing, China			1986
Scanlon et al. 2000	1,474 women 1,454 men With Mild-to-Moderate COPD Aged 35–60 years Albuquerque, NM United States and Canada			Baseline: 1988–1989 Annual follow-up for 5 years
Vollmer et al. 2000		Men	Women	NR[b]
	White	15,771	10,498	
	Black	3,308	4,403	
	Hispanic	1,604	2,239	
	Asian/Pacific Islander	2,474	0	
	American Indian	775	1,211	
	Aged 30–85 years United States			

[a]Pack-years = The number of years of smoking multiplied by the number of packs of cigarettes smoked per day.
[b]COPD = Chronic obstructive pulmonary disease.
[c]NR = Data were not reported.

smokers (more than 10 cigarettes per day). Overall, during the five-year period of the Lung Health Study, there were no differences in the rates of change in FEV_1 declines among these participants (Scanlon et al. 2000).

The presence of respiratory symptoms, particularly coughing, phlegm, and wheezing, has been associated with an accelerated decline in FEV_1 levels in cigarette smokers and nonsmokers in a number of studies (Isaksson et al. 1981a,b; Sherman et al. 1992; Burchfiel et al. 1996; Vestbo et al. 1996). Among Japanese American men in the Honolulu Heart Program who were continuous smokers, Burchfiel and colleagues (1996) found an increased risk of rapid FEV_1 declines (>60 mL/year or greater) associated with wheezing (OR = 3.9 [95 percent CI, 1.8–8.3]). However, respiratory symptoms have not been predictive of FEV_1 declines in all studies. Although Scanlon and colleagues (2000) did not find an association between respiratory symptoms and the rate of FEV_1 declines in the Lung Health Study, their ability to detect an association may have been limited because participants in this study were restricted to smokers with mild to moderate chronic airflow obstruction.

The presence of other diseases including asthma (Lange et al. 1998) and coronary heart disease (Burchfiel et al. 1996) has been associated with an accelerated FEV_1 decline among smokers. In the Copenhagen City Heart Study, Lange and colleagues (1998) followed 9,370 women and 8,136 men, 20 to 79 years of age, over a 15-year period. Except for the youngest women (20 to 39 years of age) and the oldest men (60 to 79 years of age), smokers with asthma averaged greater FEV_1 reductions than smokers without asthma. In the Honolulu Heart Program, Japanese American men with coronary heart disease who continued to smoke had an increased risk for a rapid FEV_1 decline (>60 mL/year or greater) (OR = 1.99 [95 percent CI, 0.86–4.14]).

Nutritional factors such as dietary intake (Carey et al. 1998) and anthropometric characteristics

Rate of FEV_1 decline	Type of study/comments
-6.5 mL/year of smoking in excess of decline in nonsmokers	Cross-sectional; significant interaction between smoking and occupational exposures and ambient pollution
Continuing smokers: -57.1 mL/year Intermittent quitters: -42.1 mL/year Sustained quitters: -37.1 mL/year	Randomized clinical trial
Excess decline attributed to smoking (mL/pack-year[a])	Cross-sectional

	Men	Women
White	-6	-7
Black	-4	-4
Hispanic	-3	-5
Asian/Pacific Islander	-3	NR
American Indian	-4	-5

(Burchfiel et al. 1996) have been associated with rates of FEV_1 decline. In a national sample of 2,171 British adults aged 18 through 73 years, Carey and colleagues (1998) found that current smokers who consumed the smallest quantities of fresh fruits (sources of antioxidant vitamins) over a seven-year period had a higher rate of FEV_1 decline than lifetime nonsmokers, with adjustments for social class, region, pack-years, and average fresh fruit scores (by rating consumption as more than one per day, one per day most days, once or twice per week, less than one per week, or never).

Anthropometric characteristics have been associated with a rapid FEV_1 decline among cigarette smokers (Burchfiel et al. 1996). Burchfiel and colleagues (1996) found that increasing body mass, measured by subscapular skinfold thickness, was associated with a lower risk for rapid FEV_1 declines (>60 mL/year or greater). A 10-mm increase in subscapular skinfold thickness was associated with a 30 percent decrease in the risk for a rapid FEV_1 decline (OR = 0.70 [95 percent CI, 0.55–0.88]).

The relationship between a single measure of and a subsequent rate of change in the FEV_1 level has been termed the "horse-racing effect"; a low FEV_1 level is a predictor of a rapid decline in the FEV_1 (Fletcher et al. 1976; Burrows et al. 1987). The term "horse-racing" was proposed because a low FEV_1 level at any point reflects a high rate of prior loss and hence is predictive of a future decline. As an integrated consequence of a prior decline, the FEV_1 level is also a potential marker for susceptibility to the factors driving the decline.

Burrows and colleagues (1987) proposed that a low FEV_1 level may be an early marker for identifying smokers who are susceptible to COPD. The investigators examined relationships between FEV_1 levels and other spirometric parameters and the rates of FEV_1 decline in 620 women and 475 men from Tucson, Arizona. For both men and women, a low initial FEV_1 level was not associated with a rapid FEV_1 decline. In men, however, an initially low ratio of FEV_1/FVC (less than 70 percent) was associated with a rapid FEV_1

decline; trends in women were reported to be similar but less marked, although the data were not provided. Similarly, in the Lung Health Study, Scanlon and colleagues (2000) found no differences in the rates of FEV_1 decline over four years of follow-up when comparing continuing smokers with a baseline FEV_1 in the lowest quintile (<63 mL/year) with those in the highest quintile (>61 mL/year). However, the investigators did find a significant association between the baseline FEV_1 percent predicted and the rate of decline. These findings need to be interpreted with attention to the characteristics of the study participants: middle-aged smokers with mild-to-moderate airflow obstruction. Overall, the available results suggest that various indicators of impaired ventilatory function predict subsequent FEV_1 declines.

Among cigarette smokers, bronchial hyperresponsiveness to a variety of stimuli (e.g., histamine and methacholine) has been associated with an accelerated rate of decline in FEV_1 levels (Frew et al. 1992; Rijcken et al. 1995; Villar et al. 1995; Tashkin et al. 1996). In the Lung Health Study, Tashkin and colleagues (1996) examined the relationship between bronchial hyperreactivity to methacholine and FEV_1 declines among 5,733 smokers aged 35 through 60 years with mild COPD (mean FEV_1/FVC, 65 percent; FEV_1, 78 percent predicted). After adjusting for age, gender, baseline smoking history, changes in smoking status, and baseline lung function levels, the investigators found that airway hyperreactivity during the five-year follow-up was a strong predictor of changes in FEV_1 levels percent predicted. The greatest decline of 2.2 percent predicted was in women who had the highest degree of hyperreactivity and who continued to smoke. The corresponding value in men was 1.1 percent predicted.

In addition to cigarette smoking, exposures to ambient air pollutants or workplace exposures may accelerate FEV_1 declines and increase future risks for COPD (Garshick et al. 1996; Xu and Wang 1998). For example, Xu and Wang (1998) examined the effects of smoking, urban air pollution, and workplace exposures on lung function levels in a 1986 cross-sectional survey of 8,287 randomly selected adults 40 to 69 years of age residing in Beijing, China. The investigators found that smokers had an increased reduction in FEV_1 levels of 6.5 mL for each year of smoking compared with adults who had never smoked; smokers living in residential and industrial areas with high levels of ambient pollutants had further decrements in pulmonary function.

Effects of Smoking Cessation

The beneficial effects of smoking cessation on the rates of FEV_1 decline were extensively reviewed in the 1990 Surgeon General's report. A major conclusion of that report relevant to FEV_1 declines and smoking cessation was that "cigarette smoking accelerates the age-related decline in lung function that occurs among never smokers. With sustained abstinence from smoking, the rate of decline in pulmonary function among former smokers returns to that of never smokers" (Table 4.13) (USDHHS 1990, p. 11). Since that report, there have been additional studies supporting these conclusions (Townsend et al. 1991; Anthonisen et al. 1994; Sherrill et al. 1994; Xu et al. 1994; Burchfiel et al. 1995; Frette et al. 1995; Murray et al. 1998; Berglund et al. 1999; Scanlon et al. 2000). These studies also have advanced an understanding of factors that modify the effects of smoking cessation on rates of FEV_1 decline.

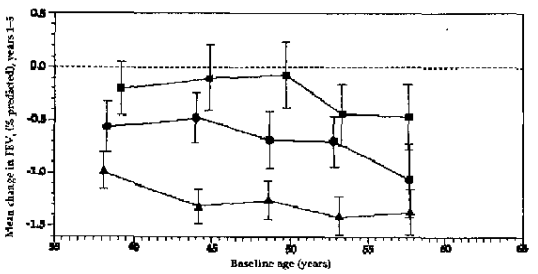
The Lung Health Study provides powerful clinical trial data on the effects of smoking cessation on the rates of FEV_1 decline and lung function levels (Anthonisen et al. 1994; Scanlon et al. 2000). This five-year, multicenter clinical trial of smoking cessation interventions was conducted in 10 North American centers. Between 1986 and 1989, 5,887 women (37 percent) and men (63 percent) aged 35 through 60 years who were current smokers with mild to moderate airflow obstruction (FEV_1/FVC of 70 percent or less and FEV_1 between 55 percent and 90 percent of predicted normal) were randomized into three groups: usual care, smoking cessation intervention with a placebo inhaler, and smoking cessation intervention with an inhaled bronchodilator (ipratropium bromide). Participants in the smoking cessation intervention (placebo group and the usual care group who stopped smoking in the first year of the trial had an average increase in FEV_1 levels of 47 mL compared with a 49 mL decrease among persons who continued to smoke (Scanlon et al. 2000). Between year one and year five of the trial, the average rate of FEV_1 reduction among continuous smokers was 62 mL/year, twice that of sustained quitters (31 mL/year) during the same time period. Quitting intermittently during the follow-up period was associated with an intermediate rate of decline (43 mL/year). The degree of improvement during the first year of cessation and the rates of FEV_1 decline after cessation varied with age at cessation, gender, amount of smoking, level of baseline lung function, and airways hyperreactivity.

Results from several investigations suggest that the benefits of smoking cessation are greatest for persons who stop smoking at younger ages (Camilli et al.

1987; Sherrill et al. 1994; Xu et al. 1994; Frette et al. 1998; Scanlon et al. 2000). In the Lung Health Study, Scanlon and colleagues (2000) found that sustained quitters younger than 50 years of age had the slowest rates of FEV_1 decline during the five-year follow-up period compared with sustained quitters 50 years of age and older (Figure 4.3). Among 147 women and 141 men who were new quitters in the prospective Tucson Epidemiological Study of Airways Obstructive Disease, Sherrill and colleagues (1994) estimated that smoking cessation among women improved FEV_1 levels by 4.3 percent at 20 years of age and by 2.5 percent at 80 years of age. For men, FEV_1 improvements were less at both ages: 1.2 percent at 20 years of age and zero at 80 years of age. During the 24 years of follow-up in the Dutch Vlagtwedde-Vlaardingen Study (Xu et al. 1994), the mean FEV_1 loss in former compared with current smokers was 20 mL/year less for women who stopped smoking before 45 years of age, but only 5.4 mL/year less for women who stopped smoking at 45 years of age or older. The corresponding values for men were 28.2 mL/year less for men younger than 45 years of age, and 10.4 mL/year less for men 45 years of age and older. In the Rancho Bernardo (California) Heart and Chronic Disease Study, 826 women and 571 men aged 51 through 95 years had spirometry testing from 1988–1991 (Frette et al. 1998). Women who were former smokers who stopped smoking before 40 years of age had FEV_1 levels similar to those for women who had never smoked (2.09 L and 2.13 L, respectively). The average FEV_1 level for women who stopped smoking at 40 through 69 years of age was 2.02 L, which was between that for female nonsmokers (2.13 L) and female current smokers (1.71 L). Women who stopped smoking at 60 years of age or older had a FEV_1 level similar to that of current smokers (1.72 L and 1.71 L, respectively); the same pattern in relation to age at smoking cessation was found for men.

Limited data suggest that smoking cessation more significantly benefits lung function and the rate of FEV_1 decline in women than in men (Sherrill et al. 1994; Scanlon et al. 2000). The Tucson Epidemiological Study of Airways Obstructive Disease (Sherrill et al. 1994) estimated that the average improvement in

Figure 4.3 Mean change and 95 percent confidence interval in forced expiratory volume in one second (FEV_1) percent predicted from years 1–5 of the Lung Health Study for sustained quitters, intermittent quitters, and continuous smokers, by quintile of age



Source: Scanlon et al. 2000, p. 387. Reprinted with permission.

FEV_1 levels at 80 years of age was higher among women who had quit smoking (2.5 percent) than among men who had stopped smoking (0.0 percent). Women who were sustained quitters in the Lung Health Study had improvements in FEV_1 levels in the first year of cessation 2.5 times greater than did men (Scanlon et al. 2000). The report from Scanlon and colleagues (2000) did not provide gender-specific effects on subsequent FEV_1 rates of decline.

The amount of exposure to cigarette smoke, which may be measured in several ways, may also influence the effects of smoking cessation (Burchfiel et al. 1995; Scanlon et al. 2000). Burchfiel and colleagues (1995) found slower FEV_1 declines after quitting in Japanese American men with the highest level of baseline smoking (-9.1 mL/year) compared with men with the lowest level (-24.1 mL/year). In the Lung Health Study, Scanlon and colleagues (2000) found no differences in the rates of FEV_1 decline among sustained quitters from year one through year five of follow-up in relation to the number of cigarettes smoked at baseline. However, they did find that the largest improvements in FEV_1 levels after smoking cessation for the first year were among persons who smoked the *most cigarettes per day before quitting (Figure 4.4)* (Scanlon et al. 2000). Among sustained quitters in the Lung Health Study, for the subgroup with the highest quintile of cigarettes smoked per day before quitting, improvement in FEV_1 levels was 3.33 percent predicted in the first year of cessation compared with only 0.51 percent predicted for the lowest smoking quintile.

Limited data are available on the relationship between the FEV_1 level at quitting and the consequences of smoking cessation (Burchfiel et al. 1995; Scanlon et al. 2000). In the Honolulu Heart Program, Burchfiel and colleagues (1995) found that after adjusting for age, height, and amount smoked, the benefits of quitting were more evident in persons with *lower* baseline FEV_1 levels. *In contrast*, Scanlon and colleagues (2000) found that a baseline FEV_1 level was not predictive of subsequent rates of decline in the FEV_1 level and baseline level was not associated with greater improvements after the first year of cessation. The conflicting results between these two studies may reflect differing study populations. The Honolulu Heart Program was population-based and began with middle-aged Japanese American men, whereas the Lung Health Study used volunteer smokers with evidence of mild-to-moderate airflow obstruction.

The degree of bronchial reactivity has been strongly associated with the magnitude of improvements in FEV_1 levels in the first year of cessation, and with the subsequent rates of FEV_1 decline. In the Lung Health Study, Tashkin and colleagues (1996) found that persons with higher airway reactivity had the greatest improvements in FEV_1 levels within the first year after quitting, whereas the slowest rates of FEV_1 decline occurred among sustained quitters with the lowest airway reactivity.

Although the benefits of smoking cessation on rates of decline and lung function levels are well established, weight gain associated with quitting may reduce lung function levels and increase FEV_1 declines, thus counterbalancing the benefits of quitting. In the Lung Health Study, Wise and colleagues (1998) found that the FVC was affected more than the FEV_1 by the weight gain. The estimated loss of FEV_1 was 11.1 mL/kg of weight gain for men and 10.6 mL/kg for women, and the mean weight gains over five years among sustained quitters were 6.4 kg and 8.8 kg, respectively. Furthermore, the average FEV_1 decline was greater in those who gained the most weight during the five years of follow-up (Figure 4.5). However, the effects of weight gain on the rates of FEV_1 decline was relatively small compared with the effects of continued smoking, and the FVC and FEV_1 would be expected to increase with weight loss.

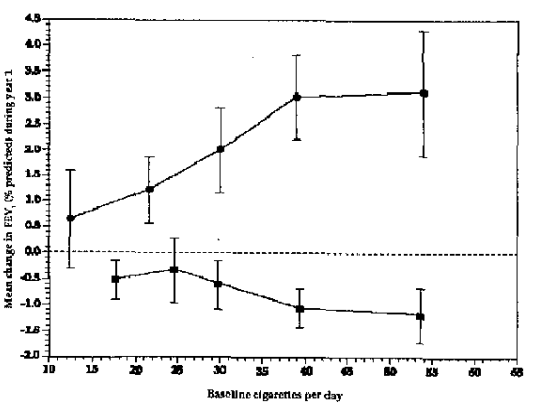
Evidence Synthesis

The adverse effects of active smoking and the benefits of smoking cessation on lung function decline have been firmly established (USDHHS 1984, 1990). Research emphasis has shifted to finding determinants of susceptibility to rapid lung function decline in active smokers and determinants of improvements after smoking cessation. Factors that predict the greatest susceptibility to rapid lung function decline while actively smoking include a greater number of cigarettes smoked, wheezing, asthma, bronchial hyperreactivity, low body mass, low lung-function level (FEV_1 percent predicted or low FEV_1/FVC), occupational exposures, and ambient air pollution. However, there is limited evidence available on how modifying active smoking affects the rate of lung function decline by gender, ethnicity, and antioxidant dietary intake.

Conclusions

1. The evidence is sufficient to infer a causal relationship between active smoking in adulthood and a premature onset of and an accelerated age-related decline in lung function.

Figure 4.4 Mean change and 95 percent confidence interval in forced expiratory volume in one second (FEV_1) percent predicted during year 1 of the Lung Health Study, for persons who quit smoking and for persons who continued to smoke during year 1, by quintile of the number of cigarettes smoked at baseline



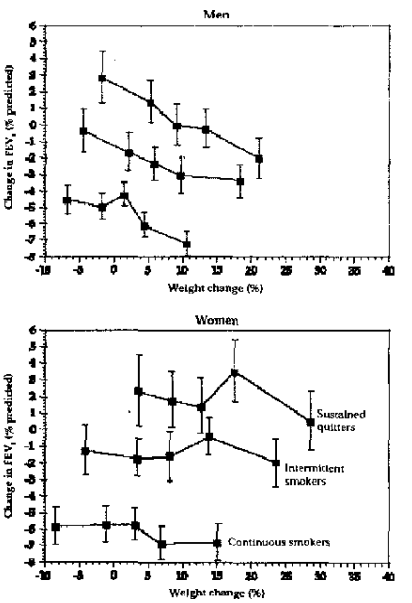
Note: Corrected data presentation shown here. When the smokers were ranked by quintile, the heaviest smokers had the largest functional losses during the first year if they continued smoking ($p = 0.028$).
Source: Scanlon et al. 2000, p. 389. Reprinted with permission.

2. The evidence is sufficient to infer a causal relationship between sustained cessation from smoking and a return of the rate of decline in pulmonary function to that of persons who had never smoked.

Implications

These conclusions provide a strong rationale for smoking cessation interventions for active smokers. The greatest benefits from smoking cessation will occur at younger ages, but all smokers benefit from cessation regardless of age. Identifying smokers with the greatest susceptibility for a rapid decline in lung function may lead to more targeted interventions, but cessation for all smokers is central to preventing COPD.

Figure 4.5 The relationship between mean changes in forced expiratory volume in one second (FEV_1) percent predicted to quintiles of mean changes in weight for each smoking category



Note: Corrected data presentation shown here. The interval for changes in FEV_1 percent predicted and weight are between baseline and the fifth annual visit. The top panel shows men and the bottom panel shows women. Error bars represent a standard error of ±2.
Source: Wise et al. 1998, p. 869. Reprinted with permission.

Chronic Respiratory Symptoms and Diseases

Substantial observational evidence has long shown that respiratory symptoms and diagnoses, the most relevant health outcomes to patients, are causally associated with smoking. Respiratory symptoms—coughing, productive coughing, wheezing, and dyspnea (difficulty breathing and shortness of breath)—are nonspecific and are associated with a number of acute and chronic respiratory diseases and even nonrespiratory diseases. Despite the nonspecificity of respiratory symptoms, their presence is a sensitive indicator of underlying lung injury and disease [Fletcher et al. 1983], and they have clinical relevance because they may impair functioning and reduce the quality of life. Selected diseases, particularly asthma and emphysema, symptoms such as wheezing, may be sufficiently specific in children to be used to define the disease. However, the specificity of wheezing for asthma declines with age because of the increasing prevalence of COPD.

Respiratory Symptoms: Childhood and Adolescence

Overall, the frequency of respiratory symptoms in children and adolescents is greater in current smokers compared with nonsmokers or former smokers, and the duration and amount of smoking further increase the frequency of symptoms [USDHHS 1994; Arday et al. 1995; Larsson 1995; Lam et al. 1998; Withers et al. 1998]. A major conclusion of the 1994 Surgeon General's report was that "Cigarette smoking during childhood and adolescence produces significant health problems among young people, including cough and phlegm production, an increased number and severity of respiratory illnesses" and "decreased physical fitness" (USDHHS 1994, p. 41). Since the 1994 report, several investigations have confirmed and extended the conclusions relevant to respiratory symptoms in childhood and adolescence (Arday et al. 1995; Lam et al. 1998; Withers et al. 1998).

Epidemiologic Evidence

To examine the relationship between smoking status and respiratory symptoms, Arday and colleagues (1995) used self-reported questionnaire data obtained from a random sample of 28,504 high school seniors in the 48 contiguous United States from 1982–1989. Compared with students who had never smoked or who had smoked only once or twice in the past, current regular smokers (i.e., reported smoking at least one cigarette within the past 30 days) who began to smoke daily by ninth grade were more likely to report at least one episode in the past 30 days of coughing spells (OR = 2.1 [95 percent CI, 1.90–2.33]), shortness of breath when not exercising (OR = 2.87 [95 percent CI, 2.38–2.99]), and wheezing or gasping (OR = 2.58 [95 percent CI, 2.29–2.89]). These risk estimates were adjusted for gender, marijuana and cocaine use, parental education, and the year of the survey. The prevalence of respiratory symptoms increased with the amount and duration of smoking.

Lam and colleagues (1998) conducted a cross-sectional survey of 6,704 students 12 to 15 years of age who were attending school in Hong Kong. Students who reported smoking more than six cigarettes per week had a higher prevalence of coughing for three months compared with students who had never smoked (OR = 3.02 [95 percent CI, 1.98–4.59]), and a higher prevalence of wheezing in the past three months (OR = 2.91 [95 percent CI, 1.59–4.26]). These risk estimates were adjusted for gender, age, area of residence, and type of housing. Statistically significant increases in the prevalence of respiratory symptoms were associated with an increased frequency of smoking.

Withers and colleagues (1998) reported results from following a cohort of 2,289 children from the ages of 6 to 8 years to 14 to 16 years of age; all were registered with 1 of 86 family practitioners in Southampton, United Kingdom. Regular smoking (i.e., smoking at least one cigarette per week during the 12 months before completing the questionnaire) was associated with a current cough (OR = 1.71 [95 percent CI, 1.21–2.43]), the onset of a cough between the surveys (OR = 1.91 [95 percent CI, 1.12–3.25]), a persistent wheeze in boys (OR = 4.35 [95 percent CI, 1.20–14.3]), and a new report of wheezing (OR = 1.65 [95 percent CI, 1.14–2.39]).

In the three investigations published since the 1994 Surgeon General's report, the prevalence of respiratory symptoms was consistently higher among cigarette smokers than among nonsmokers (Arday et al. 1995; Lam et al. 1998; Withers et al. 1998). Furthermore, limited evidence suggests that the prevalence of symptoms increases with the duration and amount of smoking (Arday et al. 1995; Lam et al. 1998). Although the results from these investigations are not directly comparable because the survey questions on smoking status and respiratory symptoms vary across studies, in three distinct settings each study shows an increase in symptom rates for children who smoke.

Other factors that may also contribute to respiratory symptoms include gender, associated diseases (e.g., atopy or asthma), passive exposure to smoking if parents or other household members smoke,

marijuana and cocaine use, ambient air pollution, workplace exposures, and socioeconomic factors. These factors have been considered to an extent in some studies. Arday and colleagues (1995) adjusted for gender, marijuana and cocaine use, and parental education. Lam and colleagues (1998) considered gender, age, area of residence, and housing type. Withers and colleagues (1998) included gender, personal and family history of atopy, passive smoking, other household exposures, and social factors. However, despite inconsistent controls for other factors that may contribute to the occurrence of respiratory symptoms, none is likely to substantially confound the strong association between smoking and respiratory symptoms.

Limited data are available on the relationship between smoking cessation and the occurrence of respiratory symptoms in children and adolescents (Arday et al. 1995; Lam et al. 1998). Compared with nonsmokers, former smokers report more frequent respiratory symptoms, but they generally have fewer occurrences of symptoms than regular smokers. Several factors may partially explain this higher occurrence in former smokers compared with nonsmokers, including a relatively short duration of cessation, false reporting of their smoking status, and the "healthy smoker" effect. This effect refers to the observation that persons who continue to smoke are less likely to have respiratory symptoms, in contrast to former smokers who quit smoking because of frequent respiratory symptoms (Weiss et al. 1989).

Evidence Synthesis

Since the 1994 Surgeon General's report on smoking and health, several investigations have been published that confirm and extend conclusions of that report that are relevant to respiratory symptoms in childhood and adolescence (Table 4.13). These studies establish that respiratory symptoms increase with the amount and duration of smoking. Further, these studies also show that the effects of active smoking on respiratory symptoms are not due to other factors that increase respiratory symptoms. Limited data are available on the effects of smoking cessation on respiratory symptoms among youth.

Conclusion

1. The evidence is sufficient to infer a causal relationship between active smoking and respiratory symptoms in children and adolescents, including coughing, phlegm, wheezing, and dyspnea.

Implication

This conclusion provides yet another strong rationale for smoking cessation interventions among youth.

Asthma. In the *Guidelines for the Diagnosis and Management of Asthma* of the National Heart, Lung, and Blood Institute (NHLBI 1997), asthma is the "most common chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. [T]n susceptible individuals, this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli" (p. 3).

Asthma is the most common chronic respiratory childhood disease, and it has been increasing in frequency in the United States and worldwide for several decades (NHLBI 1997; Warner 1999). This complex disease is associated with a number of environmental exposures, particularly aeroallergens, and with genetic susceptibility. Although the literature documenting the association between secondhand smoke exposure and childhood asthma is extensive (Cook and Strachan 1999), only a limited number of studies on active smoking and childhood asthma have been conducted (Larsson 1995; Kaplan and Mascie-Taylor 1997; Lam et al. 1998; Norman et al. 1998; Withers et al. 1998; Chen et al. 1999).

Epidemiologic Evidence. Establishing the presence of asthma in epidemiologic studies is one of the greatest challenges in investigating cigarette smoking and asthma, primarily because of the lack of an agreed-upon operational definition of asthma (Torén et al. 1993). However, during childhood and adolescence physician-diagnosed asthma and standardized questions about asthma-related symptoms (i.e., wheezing or wheezing with dyspnea) provide sufficient specificity. Asking such questions has been the main method used to examine active smoking and asthma among youth (Larsson 1995; Kaplan and Mascie-Taylor 1997; Lam et al. 1998; Withers et al. 1998; Chen et al. 1999).

Larsson (1995) examined the association between smoking and self-reported asthma incidence among 2,308 persons aged 16 through 19 years living in

Sweden. Between 1990 and 1993, the overall incidence of physician-diagnosed asthma was 1.3 percent per year, and the incidence among females was higher (1.8 percent per year) than that among males (0.9 percent per year). The risk for physician-diagnosed asthma was also higher among female smokers (OR = 2.0 [95 percent CI, 1.0–4.0]) than among male smokers (OR = 1.7 [95 percent CI, 0.8–4.8]). The risks for asthma-related symptoms and the use of asthma medications also were higher among females than among males. This analysis was limited by the lack of information on other factors associated with asthma, including personal atopy, family history of atopy and asthma, parental smoking, and other potential confounding variables.

Kaplan and Mascie-Taylor (1997) examined smoking and asthma in a cohort of 8,860 participants from England, Wales, and Scotland participating in the National Child Development Study. The analysis was based on self-reports at 16 and 23 years of age. In a univariate analysis that included males and females, regular smoking since 16 years of age was associated with reports of asthma or wheezy bronchitis between 16 and 23 years of age (OR = 1.58). Stratified or multivariate analyses, adjusting for other factors, were not performed.

In a 1994 cross-sectional survey of Hong Kong schoolchildren aged 12 through 15 years, Lam and colleagues (1998) did not find an association between active smoking and physician-diagnosed asthma. The prevalence of asthma was 8.5 percent among children who reported smoking six or more cigarettes per week compared with 8.1 percent among children who had never smoked (OR = 1.18 [95 percent CI, 0.78–1.83]).

In a cohort of persons from 2,150 households in the United Kingdom, Withers and colleagues (1998) obtained questionnaire responses on smoking behaviors and asthma from participants aged 14 through 16 years. Smoking at least one cigarette per week in the 12 months preceding the survey was not associated with physician-diagnosed asthma (26.3 percent) compared with children who did not report smoking (21.9 percent). However, the prevalence of asthma was not examined separately with greater amounts of smoking.

Norman and colleagues (1998) surveyed 1,112 Swedish eighth graders 13 to 16 years of age in 1987 and again in 1991. Overall, the incidence of self-reported asthma was 1.1 percent per year. The onset of asthma was significantly associated with current smoking (OR = 3.4 [95 percent CI, 1.2–9.8]) but not with former smoking (OR = 2.8 [95 percent CI, 0.4–23.0]).

Among 3,240 persons aged 12 through 24 years who participated in the 1994–1995 Canadian National Population Health Study, Chen and colleagues (1999) found a significant association between asthma diagnosed by a health professional and smoking, but only among females. The OR for asthma among female smokers compared with female nonsmokers, adjusted for age, was 2.18 [95 percent CI, 1.41–3.44]. Among males, the OR for smokers was 0.98 [95 percent CI, 0.56–1.70] compared with nonsmokers.

In addition to the potential ethnic role of active smoking in asthma, there is strong evidence that smoking adversely affects the course of the disease in children with asthma (Godden et al. 1994; Lam et al. 1998). Godden and colleagues (1994) examined the prevalence of respiratory symptoms and FEV$_1$ levels among 360 persons from Scotland aged 34 through 40 years, who were participants in a population-based survey as children and who had been diagnosed with childhood asthma (n = 97), wheezing with an upper respiratory infection (n = 132), or no respiratory symptoms (n = 131). In the entire group, *current* smoking was associated with an increased risk of a current wheeze (OR = 2.02 [95 percent CI, 1.15–3.52]), cough (OR = 7.24 [95 percent CI, 3.39–15.49]), and phlegm (OR = 3.06 [95 percent CI, 1.27–7.39]). The risk associated with all three respiratory symptoms was substantially lower for former smokers, and only phlegm (OR = 1.68 [95 percent CI, 1.30–10.38]) was significantly associated with past smoking. In addition, current smoking was associated with a lower mean FEV$_1$ percent predicted level (–5.54 percent [95 percent CI, –10.4 to –1.09]). In the 1994 cross-sectional survey of Hong Kong schoolchildren reported by Lam and colleagues (1998), children with asthma who smoked more than six cigarettes per week were more likely to report using asthma medications during the previous two days compared with children who had never smoked (OR = 3.07 [95 percent CI, 1.58–5.97]).

Evidence Synthesis. Although the prevalence of wheezing, an asthma-related symptom, is consistently higher in current smokers than in former smokers and nonsmokers, available investigations provide inconsistent findings on the relationship between smoking and reports of physician-diagnosed asthma. Moreover, none of the investigations have fully controlled for known risk factors for asthma. There is limited but consistent evidence that active smoking worsens the prognosis of asthma in children.

Conclusions

1. The evidence is sufficient to infer a causal relationship between active smoking and asthma-related symptoms (i.e., wheezing) in childhood and adolescence.

2. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and physician-diagnosed asthma in childhood and adolescence.

3. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and a poorer prognosis for children and adolescents with asthma.

Implications. These conclusions provide a strong rationale for preventing active smoking among children and adolescents to preclude the occurrence of asthma-related symptoms. The promotion of smoking cessation should improve the prognosis for children and adolescents with asthma who smoke. Future studies of causes of childhood asthma should include active smoking as a potential etiologic agent.

Respiratory Symptoms: Adulthood

Epidemiologic Evidence

Evidence continues to accumulate confirming the long-established causal association between active smoking and respiratory symptoms in adults. Among adults, all respiratory symptoms are strongly and consistently associated with cigarette smoking (Freund et al. 1995; David et al. 1996; Bodner et al. 1998; Forastiere et al. 1998; Butland et al. 1999), and smoking cessation reduces their frequency (Kanner et al. 1998). In the Framingham Study, Freund and colleagues (1995) found that among persons aged 45 years and older, the prevalence of a cough was higher among cigarette smokers than among nonsmokers, and the prevalence increased as the amount smoked increased. Persons who smoked more than 30 cigarettes per day were seven times more likely than nonsmokers to report a chronic cough.

Among 677 women 18 to 43 years of age who were seen for prenatal care at an East Boston clinic, David and colleagues (1996) examined the relationship between cigarette smoking and a persistent wheeze without asthma. In a multiple logistic regression model adjusting for ethnicity, parental history of asthma, educational level, and the presence of a cat or dog at home, current smokers had a fivefold increased risk (OR = 4.97 [95 percent CI, 2.46–10.1]) of a persistent wheeze compared with lifetime nonsmokers. There was no increase in this risk among former smokers (OR = 1.13 [95 percent CI, 0.50–2.55]).

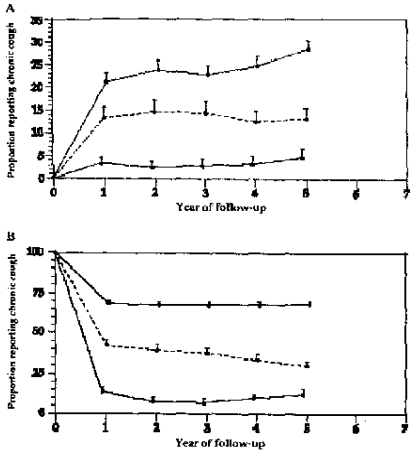
Bodner and colleagues (1998) conducted a nested case-control study of 117 adults aged 39 through 45 years with adult onset of wheezing and 277 randomly selected persons without wheezing who were participants in a population-based cohort study in Scotland. After adjusting for family history, atopy, and social class, the investigators found that current smoking was associated with adult onset of wheezing (OR = 2.0) [95 percent CI, 1.08–3.74]) and with chronic cough and phlegm (OR = 11.48 [95 percent CI, 2.49–52.89]). Former smokers were at a lower risk for adult onset of wheezing (OR = 1.48 [95 percent CI, 0.74–2.95]), but the risk remained significant for chronic cough and phlegm (OR = 5.24 [95 percent CI, 1.00–27.53]).

In a population-based study of 1,228 women aged 55 years and older living in Sonoma, California, Forastiere and colleagues (1998) examined relationships of chronic respiratory symptoms with a number of risk factors. Among women who reported shortness of breath with a wheeze or chronic wheeze during the past 12 months without a physician's diagnosis of asthma or chronic bronchitis/emphysema, the investigators found that the risk for these symptoms was highest in current smokers (OR = 3.8 [95 percent CI, 2.2–6.5]) and that the risk declined but remained statistically significant for former smokers who had quit for 10 or fewer years (OR = 1.8 [95 percent CI, 1.1–3.2]) or for more than 10 years (OR = 1.8 [95 percent CI, 1.2–2.5]). Overall, the population attributable risk for these symptoms in this population of women who had ever smoked was 35 percent.

In a longitudinal study in the Netherlands that included 782 women and 995 men, Jansen and colleagues (1999) found a dose–response relationship between the number of cigarettes smoked and the occurrence of chronic respiratory symptoms. When smokers were compared with nonsmokers, the risk (OR) of any chronic respiratory symptom was 1.89 [95 percent CI, 1.37–2.60] for those who smoked 1 to 14 cigarettes per day, 2.98 [95 percent CI, 2.14–4.29] for those who smoked 15 to 24 cigarettes per day, and 3.57 [95 percent CI, 2.32–5.48] for those who smoked 25 or more cigarettes per day. Among former smokers, the risk was lower but not statistically significant (OR = 1.23 [95 percent CI, 0.85–1.74]).

Butland and colleagues (1999) conducted a cross-sectional survey of 5,770 women and 5,582 men aged 33 years living in the United Kingdom. The prevalence of any wheezing or wheezing five or more times in the past 12 months increased with the amount smoked

Figure 4.6 Proportion (95 percent confidence interval) of participants reporting chronic cough at each annual follow-up visit, stratified by final smoking status



Note. (A) Restricted to participants who did not report the symptom of cough at entry into the study. (B) Restricted to participants who reported the symptom of cough at entry into the study.
Source. Kanner et al. 1989, p. 414. Reprinted with permission.

and was lower for former smokers. The prevalence of these symptoms was similar when comparing nonsmokers with former smokers who had quit for more than five years.

In the Lung Health Study (Kanner et al. 1989), the prevalence of all respiratory symptoms significantly decreased during the five-year sustained cessation follow-up period. Compared with current smokers, intermittent quitters had a lower prevalence of respiratory symptoms. When compared with those in the sustained cessation category, intermittent quitters had a greater prevalence of respiratory symptoms (Figure 4.6) (Kanner et al. 1989).

Evidence Synthesis

Active cigarette smoking is consistently associated with an increased risk for respiratory symptoms, including coughing, phlegm, wheezing, and dyspnea.

Moreover, the occurrence of respiratory symptoms increases with the number of cigarettes smoked and decreases with smoking cessation. These symptoms reflect the consequences of the smoking-caused changes throughout the respiratory tract.

Conclusion

1. The evidence is sufficient to infer a causal relationship between active smoking and all major respiratory symptoms among adults, including coughing, phlegm, wheezing, and dyspnea.

Implications

Respiratory symptoms are common among cigarette smokers and probably contribute substantially to an impaired quality of life and a higher utilization of health care resources. Thus, a decrease in the occurrence of these symptoms with smoking cessation will provide important benefits to public health and to the well-being of successful quitters.

Asthma. *Epidemiologic Evidence.* Asthma in adults is a complex and heterogeneous disorder likely caused by a number of occupational and environmental exposures as well as by genetic or other intrinsic predispositions. The majority of asthma begins in childhood and may result for a number of years before manifesting again in adulthood. This phenomenon may complicate the interpretation of epidemiologic investigations of risk factors for adult-onset asthma, because this condition most likely comprises both childhood asthma and true adult-onset asthma. The role of smoking as an etiologic agent in adults with asthma has been investigated in a number of studies using both longitudinal and cross-sectional designs (Tables 4.16 and 4.17). The results indicate a complicated relationship between cigarette smoking and asthma that may be modified by smoking status (i.e., current, former, or never smoker), gender, age, other established risk factors for asthma (e.g., family history of asthma or personal atopy), and the bias arising from the "healthy smoker effect" (Weiss et al. 1989).

The interpretation of the evidence for cigarette smoking and asthma is constrained by a number of methodologic considerations including varying study designs, different definitions of asthma, and different indexes for defining smoking status. Although the longitudinal design is the strongest for investigating the relationship between smoking and adult-onset asthma, the studies that have been conducted arrived at conflicting results (Table 4.16). In those studies, current smoking was associated with an increased risk of asthma among men (Vesterinen et al. 1988) and among men and women aged 40 years or older (Krzyzanowski and Lebowitz 1992). However, neither Vesterinen and colleagues (1988) nor Troisi and colleagues (1995) found an association between current smoking and asthma in women. Furthermore, Troisi and colleagues (1995) did not find a dose-response relationship between the amount smoked and asthma. The strongest associations between smoking and asthma were reported by Strachan and colleagues (1996) and Plaschke and colleagues (2000). However, their results are difficult to interpret. For example, Strachan and colleagues (1996) combined asthma with wheezy bronchitis, and Plaschke and colleagues (2000) did not define "smokers," which may have included former smokers. Finally, McWhorter and colleagues (1989) only examined ever smoking in their longitudinal investigation and did not find an association with asthma.

A number of cross-sectional studies have examined the association between asthma and smoking, with inconsistent results for both current and former smokers (Table 4.17). Of the 10 publications that provided quantitative results, 3 found an association between current smoking and asthma in men and women (Ben-Noun 1999; Chen et al. 1999; Torén and Hermansson 1999), and 1 found an association in only in women (Siroux et al. 1999). No association was reported in [illegible] national studies (Flodin et al. 1995; Daw[illegible] 1996; Bodner et al. 1998; Forastiere et al. 1998; Zhang et al. 1999; de Marco et al. 2000; Chen et al. 2001). More[illegible] two investigations provided indirect evidence that current smoking is not associated with asthma (Hansen et al. 1999; Hjalmarsson et al. 2001), and limited data suggest that the risk of asthma may be greater because of a family history of asthma or the presence of other atopic conditions (i.e., hay fever, atopic dermatitis) (Melbostad et al. 1998; Torén and Hermansson 1999). However, this finding was contradicted by the results reported by Plaschke and colleagues (2000).

Among former smokers, an association with asthma has been inconsistent (Table 4.17). Out of nine studies, five found an increased risk for asthma among former smokers compared with current smokers (Flodin et al. 1995; Troisi et al. 1995; Bodner et al. 1998; Forastiere et al. 1998; Siroux et al. 2000), with ORs ranging from [illegible] to [illegible]. Four studies found no association (Daw[illegible] et al. 1996; Chen et al. 1999; de Marco et al. 2000; Hjalmarsson et al. 2001).

In four cross-sectional studies that examined ever smokers, defined as current and former smokers, (Table 4.17) (Flodin et al. 1995; Melbostad et al. 1998; Ben-Noun 1999; Siroux et al. 2000), three of the studies

associated asthma with ever smoking (Flodin et al. 1995; Melbostad et al. 1998; Ben-Noun 1999) with ORs ranging from 1.3 to 1.9.

Investigating the relationship between smoking and asthma offers a number of challenges, including diagnostic misclassifications and changes in smoking behaviors because of asthma. Dodge and colleagues (1985) found that among persons aged 40 years or older with newly diagnosed asthma, emphysema, or chronic bronchitis based on self-reports, women were more likely than men to receive a physician's diagnosis of asthma or chronic bronchitis, and men were more likely to receive a diagnosis of emphysema. In the Nurses Health Study, Troisi and colleagues (1995) found that among women diagnosed with chronic bronchitis, smokers were more likely to receive a subsequent diagnosis of asthma than were nonsmokers (RR = 2.02 [95 percent CI, 1.01–4.02]). This labeling pattern in women may tend to bias toward an association of asthma with smoking.

Because the bronchial hyperresponsiveness of asthma may cause an intolerance to tobacco smoke, and because smoking worsens respiratory symptoms in persons with asthma (Althuis et al. 1999; Sippel et al. 1999), some persons alter their smoking habits and thereby obscure a possible causal association (Weiss et al. 1989). The result is that persons with asthma may not start smoking or may be more likely to quit, a phenomenon referred to as the "healthy smoker effect" (Weiss et al. 1989); however, few data support these suggested biases. In a population-based survey of 3,019 persons from Australia, Wakefield and colleagues (1995) found no differences in the prevalence of smoking between persons with asthma (28.5 percent) and persons without asthma (26.9 percent), or in the amount smoked. Moreover, there were no differences between those two groups in reports of ever trying to quit or trying to quit in the past year.

Siroux and colleagues (2000) examined smoking behaviors among 200 adult patients with asthma and 265 controls without asthma, and found that childhood asthma was not associated with a reduced initiation of smoking. However, patients with asthma were more likely than those without asthma to quit smoking (OR = 2.76 [95 percent CI, 1.19–6.42] for men; OR = 2.26 [95 percent CI, 1.11–4.34] for women).

Surrogate evidence for a link between cigarette smoking and asthma may be obtained from investigations of the relationship between smoking and nonspecific bronchial hyperresponsiveness (Weiss et al. 1989). Although the results are not entirely consistent, available evidence suggests that current smokers have greater bronchial hyperresponsiveness compared with nonsmokers, thus establishing a biologically plausible link for a causal role for smoking in the development of asthma (Weiss et al. 1989; Kennedy et al. 1990; Rijcken et al. 1993; Sunyer et al. 1997).

A possible biologic link between smoking and asthma was also described by Wang and colleagues (2001) in their case-control study of 128 patients with asthma and 136 controls, identified through a community-based survey of 10,014 patients in China. Patients and controls were all examined for the prevalence of two genetic variations of the β_2 adrenergic receptor gene, which controls airway dilatation. Compared with lifetime nonsmokers, ever smokers who were homozygotes for a specific genetic variation of the β_2-adrenergic receptor gene on chromosome 16 (arginine/arginine-16) had a markedly increased risk for asthma (OR = 7.81 [95 percent CI, 2.07–29.5]). In addition, there was a strong dose-response relationship with the amount smoked.

Although the relationship between active smoking and adult-onset asthma is inconsistent, there is consistent evidence that smoking adversely affects the control and severity of asthma (Prescott et al. 1997; Cassino et al. 1999; Siroux et al. 2000; Beeh et al. 2001). As part of the Copenhagen City Heart Study, Prescott and colleagues (1997) examined 13,540 patients for factors associated with hospital admissions for asthma between 1977 and 1993. Overall, the risk of hospitalization for asthma was 20 percent greater in current and former smokers compared with lifetime nonsmokers (95 percent CI, 1.1–1.4) for each 10-year period of smoking. Cassino and colleagues (1999) examined determinants of emergency department visits for asthma among 1,216 adults with asthma living in New York City. Compared with nonsmokers, the RRs for emergency department visits were 1.07 (95 percent CI, 0.97–1.18) for 1 to 5 pack-years of smoking, 1.69 (95 percent CI, 1.56–1.84) for 6 to 13 pack-years, 0.93 (95 percent CI, 0.84–1.04) for 14 to 30 pack-years, and 1.11 (95 percent CI, 1.00–1.22) for 31 or more pack-years. They also identified heavy cigarette use (13 or more pack-years) as a predictor of emergency department visits following days that had high outdoor ozone levels. In a case-control study of 200 adults with asthma from six specialty clinics in France and 265 controls without asthma, Siroux and colleagues (2000) found that active smoking was associated with an increase in asthma severity. For example, compared with nonsmokers, current smokers more often reported one or more asthma attacks per day (OR = 2.39 [95 percent CI, 1.06–5.36]) and abnormal breathing between attacks (OR = 2.06 [95 percent CI, 0.97–4.36]) than nonsmokers. Among 112 persons with asthma seen at a pulmonary

Table 4.16 Longitudinal studies on the association between smoking and adult asthma

Study	Population	Period of study/follow-up
Vesterinen et al. 1988	7,274 wom[illegible] 7,371 men Aged 18-[illegible] Finland	Baseline: 1975 Follow-up: 1981
McWhorter et al. 1989	9,212 women, 8,037 men Aged [illegible]-74 years [illegible] States	Baseline: [illegible] Follow-up: 1985
Krzyzanowski and Lebowitz 1992	6,816 women, 7,294 men Aged 19-70 years Cracow, Poland 839 women, 613 men Aged 19-70 years Tucson, Arizona	Baseline: [illegible] Tucson: 1972 Follow-up: 4 years
Troisi et al. 1995	74,092 women Aged 34-[illegible] The [illegible]	Baseline: 1976 Follow-up: [illegible] years
Strachan et al. 1996	18,[illegible] participants in the [illegible] Scotland and Wales	Baseline: 1[illegible] Follow-up: 1[illegible]
Plaschke et al. 2000	650 women, 650 men Aged 20-[illegible] years Zone [illegible]	Baseline: [illegible] Follow-up: 1[illegible]

[a]OR = Odds ratio.
[b]CI = Confidence interval.
[c]Ages at which persons were asked if they currently smoked.

Findings (OR*)		Asthma definition/comments
	OR (95% [illegible] compared with never smokers	Self-reported physician-diagnosed asthma
Smoking status	Women	
Former smoker	[illegible]	
Current smoker	[illegible]	
	OR (95% CI) compared with never smokers	Self-reported physician-diagnosed asthma
Smoking status	New cases/1,000 children	
Ever smoked	1.3 (0.8–2.2)	
	Asthma incidence rate ratio (continuous smokers vs. nonsmokers)	Physician-diagnosed bronchial asthma
Age (years)	Women	Men
19–40	0.6	0.8
41–55	1.9	2.2
56–70	2.1	3.1
Amount smoked	Ages-[illegible] ever-smoked asthmatics (95% CI) compared with [illegible]	Physician-diagnosed asthma, persistent bronchitis, [illegible]
1–14 cigarettes/day	[illegible]	
15–24 cigarettes/day	[illegible]	
≥25 cigarettes/day	[illegible]	
Smoking ages†	[illegible] compared with nonsmokers	[illegible]
10–14 and 15–19 years	[illegible]	
10–14 and 15–24 years	[illegible]	
Sensitization to allergens	Asthmatics	Self-reported physician-diagnosed asthma, current asthma, [illegible]
All subjects	[illegible]	
Atopic smokers	[illegible]	
Nonatopic smokers	[illegible]	

Table 4.17 Cross-sectional studies on the association between smoking and adult asthma

Study	Population	Period of study
Flodin et al. 1995	79 persons with asthma Aged 20–65 years 304 population controls Sweden	1990
[illegible]	[illegible]	[illegible]
Davis[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]
Forastiere et al. 1994	[illegible]	[illegible]
Nielsen et al. 1998	2,904 women and 2,685 men Aged 20–70 years Norway	1991
Jaakkola et al. 1999	143 persons with asthma and [illegible] controls matched for sex and age Aged 18–65 years Israel	1996
Chen et al. 1994	[illegible]	[illegible]

[illegible]
CI = Confidence interval.
IRR = Incidence rate ratio.

Findings		Asthma definition/comments
Smoking status	Adjusted OR* (95% CI) compared with nonsmokers	Lung specialist determination based on clinical history and bronchial hyperresponsiveness, adjusted for age, gender, atopy, passive smoking, and occupational exposure
Ever smoked	1.9 (1.1–3.4)	
Current smokers	0.7 (0.4–[illegible])	
Former smokers	3.3 [illegible]	
Smoking status	RR (95% CI)	Physician-diagnosed asthma
Current smokers	0.97 (0.48–2.01)	
Former smokers	0.91 (0.49–1.72)	
Smoking status	OR (95% CI) compared with nonsmokers	Self-reported physician-diagnosed asthma, adjusted for family history of asthma, education, and history of asthma when current wheeze was in the home
Former smokers	[illegible]	
Current smokers	[illegible]	
Smoking status	OR (95% CI) compared with nonsmokers	Physician-diagnosed asthma and wheeze, adjusted for age, sex, family history of asthma, and social class
Current smokers	[illegible]	
Former smokers	[illegible]	
Smoking status	OR (95% CI)	Physician-diagnosed asthma and wheezing in the past 12 months, adjusted
Nonsmokers	1.0	
Current smokers	[illegible]	
Former ≤10 years	[illegible]	
Former >10 years	[illegible]	
Smoking status	OR (95% CI) compared with nonsmokers	Physician-diagnosed asthma, adjusted for gender, parental history of asthma, childhood asthma, and Hanover respiratory
Never smoked	1.0	
Ever smoked	[illegible]	
Smoking status	[illegible]	Asthma in family members were not [illegible]
Current smokers	[illegible]	
Ex-smokers	[illegible]	
Age at smoking status	OR (95% CI) comparing asthmatics with nonsmokers	Asthma cases diagnosed by a health professional, adjusted for age
10–24 years	Females	Males
Nonsmokers	1.0	1.0
Current smokers	[illegible]	[illegible]
Former smokers	[illegible]	[illegible]
≥25 years		
Nonsmokers	1.0	1.0
Current smokers	[illegible]	[illegible]
Former smokers	1.16 (0.95–1.63)	[illegible]

Table 4.17 Continued

Study	Population	Period of study
Torén and Hermansson 1999	8,044 women and [illegible] men Aged 20–50 years Sweden	1993
Zhang et al. 1999	[illegible]	1996
de M[illegible] 2000	[illegible]	[illegible]
Hanssen et al. 2000	[illegible]	[illegible]
Tunnicliffe et al. 2000	200 persons with asthma, 265 nonasthmatic controls Mean ages 40.1 and 42 years France	Data were not reported
Kilpeläinen et al. 2001	8,503 women and [illegible] men Aged 15–[illegible] years Finland	[illegible]
Kotaniemi et al. 2001	3,938 women and [illegible] men Aged 20–69 years Finland	1995

[illegible]
FEV_1 = Forced expiratory volume in 1 second.

Findings		Asthma definition/comments
Smoking status	OR (95% CI) compared with nonsmokers	Physician-diagnosed asthma; adjusted for gender and age
Nonsmokers	1.0	
Current smokers	1.3 (1.05–1.6)	
Current with hay fever	4.0 (2.9–5.7)	
Current with atopic dermatitis	2.7 (1.6–4.4)	
Amount smoked	OR (95% CI) compared with nonsmokers	Physician-diagnosed asthma; adjusted for age, area of residence, duration of residence in the area, occupation, [illegible]
Nonsmokers	1.0	
<10 cigarettes/day	0.81 (0.30–2.20)	
10–20 cigarettes/day	1.26 (0.97–2.80)	
>20 cigarettes/day	1.7 (1.1–3.76)	
Smoking status	Adjusted OR (95% CI) compared with nonsmokers	Physician-diagnosed asthma; adjusted for age, area of residence, occupation, and [illegible] gender and BMI level
Nonsmokers	1.0	
Current smoker	1.52 (0.98–2.41)	
Former smoker	0.91 (0.56–1.48)	
Survey years	Asthma prevalence among nonsmokers	Asthma prevalence among current smokers	Current, former smokers and never smokers were classified according to [illegible]
1976–1978	1.8%	3.0%	
1991–1994	1.8%	4.0%	
Smoking status	Adjusted OR (95% CI)		A positive response to having had attacks of breathlessness at rest, exercise, or at least 1 asthma attack, accompanied by wheezing in the past 12 months and a physician diagnosis or a response to question based on a clinical [illegible] and [illegible], and city
	Men	Women	
Ever smoked	1.21 (0.55–2.65)	1.19 (0.60–2.36)	
Former smokers	2.20 (1.1–4.34)	2.76 (1.19–6.42)	
Current smoking was not [illegible]			Physician-diagnosed asthma; no gender information was reported
Smoking status	OR (95% CI) compared with nonsmokers		Physician-diagnosed asthma
Nonsmokers	1.0		
Current smokers	0.[illegible]		
Former smokers	1.24 (0.93–1.61)		

specialist practice in Germany. Beeh and colleagues (2003) found that severe asthma, defined as a FEV_1 less than 60 percent predicted, was strongly associated with current smoking (OR = 4.8 [95 percent CI, 1.3–18.3]).

Evidence Synthesis. Although limited evidence suggests that smoking is a biologically plausible cause of asthma, the available epidemiologic evidence of an association between smoking and adult-onset asthma is inconsistent (Tables 4.16 and 4.17). A number of methodologic limitations, including different definitions of asthma, different study designs, and biases such as recall bias and healthy smoker bias, probably contribute to the inconsistent results. In contrast to studies on the causation of asthma, smoking is consistently associated with a greater severity of asthma and increased use of emergency and hospital services. By increasing the degree of airways inflammation, smoking may worsen the inflammatory process that is considered central in the pathogenesis of asthma. The impairment of airways function caused by smoking may also increase the likelihood of more severe asthma on a clinical basis.

Conclusions

1. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and asthma in adults.
2. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and increased nonspecific bronchial hyperresponsiveness.
3. The evidence is sufficient to infer a causal relationship between active smoking and prior asthma control.

Implications. Because of the large numbers of persons with asthma and an increasing prevalence of asthma worldwide, the potential role of active smoking in the causation of asthma has major public health implications. Therefore, this problem is highly relevant for further research despite methodologic challenges. Patients with asthma need to be strongly encouraged to quit smoking.

COPD. COPD is defined differently by clinicians, pathologists, and epidemiologists, each discipline uses different criteria based on physiologic impairments, pathologic abnormalities, and symptoms (Sanet 1999). The hallmark of COPD is airflow obstruction based on spirometric testing, with a persistently low FEV_1 and a low ratio of FEV_1/FVC despite treatment. Clinicians often diagnose COPD when an adult cigarette smoker presents with chronic dyspnea, coughing, and consistent spirometric abnormalities.

Chronic bronchitis and emphysema with airflow obstruction are both included in the clinical syndrome of COPD. Other specific diseases associated with airflow obstruction, such as asthma, bronchiectasis, and cystic fibrosis, are specifically excluded from the clinical definition of COPD, although there may be overlapping clinical features. Chronic bronchitis and emphysema have specific definitions although the terms are used more loosely in clinical practice. Chronic bronchitis is characterized by a chronic cough productive of sputum with airflow [illegible] section. Emphysema is defined as "a condition of the lung characterized by abnormal permanent enlargement of the airspaces distal to the terminal bronchiole [illegible] panied by destruction of their [illegible] and without obvious fibrosis" (American Thoracic Society 1987, p. 225). On the basis of this definition, the diagnosis of emphysema requires an examination of gross or microscopic lung specimens or an assessment of the lungs based on computed tomography, a recently developed tool (Thurlbeck 1994).

Epidemiologic Evidence. In epidemiologic studies, the diagnosis of COPD may be derived from surveys or clinical databases. Questionnaire responses that may be used to diagnose COPD include reports of symptoms (e.g., dyspnea, coughing, or phlegm), reports of physician diagnoses (e.g., emphysema, chronic bronchitis, or COPD), or both. Spirometry is often performed in epidemiologic studies to provide objective evidence of airflow obstruction in persons with or without symptoms. Sources of data for descriptive or analytic studies of COPD include data sets containing hospital discharge information or vital statistics (e.g., from death certificates). However, the quality of these data sources may [illegible] terms used for COPD in the tabulation of terms from the International [illegible] Revision, such as "chronic bronchitis [illegible] physema" (code 492), or "chronic [illegible] not elsewhere classified" (code 496 [illegible] HS 1980b).

Cigarette smoking as a cause of COPD has been reviewed extensively in earlier reports of the Surgeon General (Table 4.13) (USDHHS 1984, 1989, 1990). A considerable amount of more recent research on the relationship between COPD and cigarette smoking has focused on determining predictors of susceptibility, as

discussed previously, and on early detection. The following discussion summarizes more current key research on the epidemiology of COPD.

COPD Morbidity. COPD is a common chronic disease in the United States and a major cause of morbidity associated with limitations on physical functioning and a high utilization of medical care services (Verbrugge and Patrick 1995; Mapel et al. 2000). Approximately 10 million people in the United States have been diagnosed with COPD (Wise 1997). Verbrugge and Patrick (1995) used data collected from the National Health Interview Survey conducted from 1983 1985 to calculate the prevalence of chronic conditions in the United States and to determine their relative impact on functioning. Among adults aged 18 years and older the prevalence of COPD, which included chronic bronchitis, emphysema, and asthma, was consistently among the top 10 chronic conditions. The prevalence was highest in men and women aged 65 years and older (16.7 percent among men and 12.6 percent among women), intermediate for men and women aged 45 through 64 years (8.8 percent and 11.4 percent, respectively), and lowest for men and women aged 18 through 44 years (5.5 percent and 9.3 percent, respectively). In addition, COPD consistently ranked among the top 10 conditions in all age groups that resulted in limitations on job-related responsibilities and other activities of daily living.

More recent national data are available from the Third National Health and Nutrition Examination Survey (Mannino et al. 2003). This survey included 20,050 U.S. adults who participated from 1988–1994 and who completed an examination that included spirometry and respiratory health questions. The findings suggest that COPD occurs frequently in the United States. The authors categorized current obstructive lung disease as a report of current asthma, bronchitis, or ever having a diagnosis of emphysema. A prior but not current diagnosis of either chronic bronchitis or asthma was categorized as past obstructive lung disease. With these definitions, obstructive lung disease was found to affect 12.5 percent of current smokers, 9.4 percent of former smokers, and 5.8 percent of lifetime nonsmokers.

COPD is associated with high medical care utilization rates, including office based physician visits and hospitalizations (Verbrugge and Patrick 1995; Sullivan et al. 2000). In the 1985 National Ambulatory Medical Care Survey, COPD was consistently among the top 10 conditions leading to a physician visit. Verbrugge and Patrick (1995) found that the largest percentage of physician visits for COPD were among men and women aged 65 years and older (10.8 percent among men and 9.4 percent among women). Intermediate for men and women aged 45 through 64 years (8.1 percent and 8.2 percent, respectively), and lowest for men and women aged 18 through 44 years (3.4 percent and 4.8 percent, respectively). In 1995, more than 16 million visits were made to physicians' offices for COPD, a 72 percent increase from 1985 (Sullivan et al. 2000). In contrast to other chronic conditions (e.g., cancer or cardiovascular disease), COPD was a less common primary cause of hospitalization in the 1994 National Hospital Discharge Survey (Verbrugge and Patrick 1995), but in 1995 it accounted for more than 500,000 hospitalizations in the United States (Sullivan et al. 2000). However, COPD often is a comorbid condition associated with other chronic conditions, including cancer and cardiovascular diseases (Ferrer et al. 1997; Mapel et al. 2000). Total estimated costs associated with COPD in 1993 were $23.9 billion, or about $1,522 per person per year, three times the per capita cost of asthma (Sullivan et al. 2000).

More recent epidemiologic investigations continue to provide strong evidence for the causal link between active smoking and COPD (Troisi et al. 1995; Forastiere et al. 1998). In the Nurses Health Study, a prospective cohort study of 74,072 women aged 34 through 68 years, the RR for self-reported, physician-diagnosed chronic bronchitis among current smokers compared with women who had never smoked was 2.85 (95 percent CI, 2.45–3.32) (Troisi et al. 1995). Forastiere and colleagues (1998), in a population based cross-sectional survey of 1,226 women aged 55 years and older, found a marked increase in risk for self-reported, physician-diagnosed chronic bronchitis/emphysema among current smokers compared with former and lifetime nonsmokers (OR = 6.4 [95 percent CI, 3.2–12.6]).

Smoking Cessation and COPD Mortality. Although smoking cessation slows the rate of FEV_1 decline, thus decreasing the risk for developing chronic airflow obstruction (Figure 4.1), the risk may not return to that for nonsmokers. In a population-based study of 1,391 Seventh-Day Adventists from California, which included nonsmokers and former smokers (aged 16 years or older), Berglund and colleagues (1999) found that, compared with never smoking, past smoking for 10 years was associated with a small but significant risk (OR = 1.29 [95 percent CI, 1.00–1.66]) of airflow obstruction (FEV_1/FVC less than 65 percent or FEV_1 percent predicted less than 75 percent).

The risk of self-reported physician-diagnosed chronic bronchitis returns close to that of nonsmokers, but only after 5 to 10 years of cessation (Troisi et al. 1995; Forastiere et al. 1998). In the Nurses Health Study, Troisi and colleagues (1995) found that among former smokers the incidence of chronic bronchitis among women was equal to the incidence in those who had completely abstained from smoking for five or more years. Among women aged 55 years and older from Sarcoma, California, Forastiere and colleagues (1998) found that the occurrence of physician-diagnosed chronic bronchitis/emphysema was higher in former smokers who had stopped smoking for 10 years or less (OR = 4.7 [95 percent CI, 2.5–8.7]) compared with nonsmokers, but the risk returned close to that of nonsmokers after more than 10 years of cessation (OR = 1.6 [95 percent CI, 0.9–2.8]).

COPD Mortality. In 2001, COPD (excluding asthma) was the fourth leading cause of death in the United States with more than 118,000 deaths (4.9 percent of all deaths) and an overall mortality rate of 41.7 per 100,000 (Arias et al. 2003). Over the past 50 years, the age-adjusted mortality rate from COPD has been increasing. Of the 10 leading causes of death in the United States, only COPD has increased during this period (Wise 1997). Factors that contribute to the rising COPD mortality rates include decreasing mortality from other causes of death (e.g., cardiovascular diseases) and increasing mortality among women and nonwhite males (Mannino et al. 1997).

Although COPD prevalence and mortality rates since the late 1970s have been substantially higher in men than in women, the estimated percentage increases have been higher for women (Thun et al. 1996, 1997a; Mannino et al. 1997). In fact, from 1979–1988 mortality rates for men and physicians either remained stable or decreased (Brown et al. 1994). These patterns may be partially explained by differences between the prevalence of smoking and smoking behaviors in women and men that have occurred over time. During the past 20 to 30 years, the prevalence and amount of smoking among women have become increasingly similar to those of men (USDHHS 2001).

The prospective studies of the American Cancer Society (Cancer Prevention Study I [CPS-I] and Cancer Prevention Study II [CPS-II]), which were conducted in the early- to mid-1960s and in the 1980s, provide evidence for a marked increase in the risk of mortality from COPD among women (Thun et al. 1996, 1997a). In CPS-II the death rate for female current smokers (61.6 per 100,000 person-years) was three times higher than in CPS-I. The mortality RR was 12.8 for female current smokers compared with women who had never smoked. For male current smokers in CPS-II, the death rate (103.9 per 100,000 person-years) was 41 percent higher than for male current smokers in CPS-I. The mortality RR was 11.7 for male current smokers compared with men who had never smoked.

Thun and colleagues (1997b) examined mortality rates for COPD in CPS-II in relation to the number of cigarettes currently smoked at baseline. The RR for death from COPD increased with the number of cigarettes smoked per day. For female current smokers compared with women who had never smoked, the RR was 5.6 for 1 to 9 cigarettes per day, 11.0 for 10 to 19 cigarettes per day, 21.2 for 20 cigarettes per day, 22.9 for 21 to 39 cigarettes per day, and 31.4 for more cigarettes per day. The corresponding risks for current male smokers compared with men who had never smoked were 8.8 for 1 to 9 cigarettes per day, 8.9 for 10 to 19 cigarettes per day, 10.4 for 20 cigarettes per day, 16.5 for 21 to 39 cigarettes per day, and 19.0 for 40 or more cigarettes per day.

Using CPS-I and CPS-II data on the RR of COPD mortality, Thun and colleagues (1997a,b) calculated the percentage of COPD deaths attributable to cigarette smoking. Among women in CPS-I, 85 percent of COPD deaths were attributable to smoking; this percentage increased to 92.2 percent in CPS-II. The corresponding values among men were 89.2 percent and 91.4 percent, respectively.

Mannino and colleagues (1997) analyzed mortality trends for obstructive lung disease (including asthma) among people who died in the United States from 1979–1993. Of all the deaths during this period, 8.2 percent had obstructive lung disease listed on the death certificate, but in only 43.5 percent was the death attributed to obstructive lung disease as the time of the study, the age-adjusted mortality rates for obstructive lung disease were highest in whites (ranging from 98.8 to 115.5 per 100,000 per year), followed by black men (77.5 to 100.2 per 100,000), men of other races (38.1 to 58.6 per 100,000), white women (25.5 to 57.7 per 100,000), [illegible] women (11.9 to 36.3 per 100,000), and women [illegible] per 100,000). The percentage increases in rates were highest for black women, [illegible] followed by white women (121 percent), white men (87 percent), black men (29.3 percent), and lowest among white men (15.9 percent).

Smoking Cessation and COPD Mortality. The literature on the effects of smoking cessation on mortality from COPD was extensively reviewed in the 1990 Surgeon General's report and the major conclusion relevant to mortality from that report was "With sustained abstinence, the COPD mortality rates among former smokers decline in comparison with continuing smokers" (Table 4.13) [USDHHS 1990, p. 11]. However, the risk of COPD mortality among former smokers, even after 20 years or more of abstinence, remains elevated compared with the risk among people who have never smoked. Moreover, within approximately the first five years of cessation, mortality rates from COPD initially increase above the rates for continuing smokers and then gradually decline with an increase in the duration of abstinence.

Evidence Synthesis. The recent literature on smoking and COPD provides further support for the conclusion of the 1984 Surgeon General's report that "cigarette smoking is the major cause of COLD in the United States for both men and women. The contribution of cigarette smoking to COLD morbidity and mortality far outweighs all other factors" (USDHHS 1984, p. 8). Whereas the risks for COPD morbidity and mortality decline with smoking cessation, they may not return to the levels of nonsmokers, probably because smoking has resulted in irreversible injury to the airways and parenchyma. A growing body of literature in recent years is providing evidence for major socioeconomic consequences of COPD associated with a marked increase in the utilization of medical care resources.

Conclusion

1. The evidence is sufficient to infer a causal relationship between active smoking and chronic obstructive pulmonary disease morbidity and mortality.

Implication. COPD represents a major public health problem that is increasing but could be almost completely prevented with the elimination of smoking.

Cigarette Type and Risk for Chronic Respiratory Diseases. The effect of cigarette type on respiratory symptoms and COLD was reviewed in the 1984 Surgeon General's report by Samet (1986), and by the National Cancer Institute (NCI) Tobacco Control Monograph 13 (NCI 2001). A conclusion from the 1984 report was as follows:

> Although a reduction in cigarette tar content appears to reduce the risk of cough and mucus hypersecretion, the risk of shortness of breath and airflow obstruction may not be reduced. Evidence is unavailable on the relative risks of developing COLD consequent to smoking cigarettes with the very low tar and nicotine yields of current and recently marketed brands (USDHHS 1984, p. 12).

Since the publication of that report, few new data are available on the relationship between cigarette type and chronic respiratory diseases (Lange et al. 1990, 1992).

Epidemiologic Evidence. Using longitudinal spirometric data obtained during five years (1978–1978 and 1981–1983) from 4,372 smokers and 3,753 nonsmokers who participated in the Copenhagen City Heart Study, Lange and colleagues (1990) examined the relationship between cigarette type (filter-tipped versus unfiltered) and lung function deterioration. Overall, there was no significant difference in FEV_1 reductions among filter-tipped cigarette smokers compared with unfiltered cigarette smokers. On average, during the time of the study the tar content of Danish unfiltered cigarettes was 35 mg per cigarette compared with 23 mg per cigarette for filter-tipped cigarettes.

Lange and colleagues (1992) also examined risks of COPD mortality associated with the type of cigarette smoked (filter-tipped versus unfiltered) and inhalation patterns in 7,702 women and 6,511 men who participated in the Copenhagen City Heart Study. The RRs for COPD-related mortality differed little between women and men based on the type of cigarette smoked. Compared with women who were nonsmokers, women who smoked unfiltered cigarettes had a RR for COPD-related mortality of 15 (95 percent CI, 3.1–65.0), and women who smoked filter-tipped cigarettes had a RR of 16 (95 percent CI, 3.6–70.0). The corresponding RRs for men were 6.4 (95 percent CI, 2.0–20.0) and 7.9 (95 percent CI, 2.3–27.0), respectively.

In four prospective cohort studies in the United Kingdom, Tang and colleagues (1995) assessed mortality in 36,225 men for smoking-induced diseases, comparing filter-tipped and unfiltered cigarettes and estimated tar yields. The mortality risk for COPD was somewhat lower for smokers of filter-tipped cigarettes, but not significantly in comparison with smokers of unfiltered cigarettes. For a tar reduction of 15 mg per cigarette, Tang and colleagues (1996) estimated that COPD mortality would drop by about 20 percent, but this estimate was quite imprecise.

Histopathologic findings have also been reported that provide insights concerning tar and nicotine yields, respiratory symptoms, and lung function levels. Auerbach and colleagues (1979) quantitated smoking-related changes in the autopsied lungs of men from a Veterans Administration hospital in New Jersey. In a rigorously studied series of autopsied lungs, these investigators showed that smokers from a period when cigarettes had comparatively high tar and nicotine yields (1955–1960) had more changes in the airways at various smoking levels compared with smokers from a later period (1970–1977). They interpreted this temporal pattern as an indication that cigarettes with lower tar and nicotine yields had fewer effects on the lungs than did higher-yield cigarettes.

A number of studies have shown that smokers of lower-yield cigarettes have comparatively lower rates of respiratory symptoms (Table 4.18). Respiratory questionnaire data collected in the late 1970s from approximately 8,000 Pennsylvania women are illustrative (Schenker et al. 1982). The brand of cigarettes currently smoked was identified and used with Federal Trade Commission tar yield information to classify the smokers according to tar exposure. A higher-tar yield was positively associated with coughing and phlegm but not with wheezing or shortness of breath. For coughing and phlegm, there were consistent exposure-response relationships with an approximate doubling of symptom frequency from the lowest to the highest exposure category. The findings of other studies are similar. For example, a large study of civil servants in the United Kingdom, the Whitehall Study, showed that the percentage of smokers reporting phlegm increased with tar yield within each stratum of cigarettes smoked per day, even the lowest (Higenbottam et al. 1980).

Not all studies show less disease associated with lower-yield cigarettes (Table 4.18). One study from Finland found that symptom levels in young smokers who were just initiating smoking did not depend greatly on tar yield (Rimpela and Teperi 1989). In this six-year follow-up study, the youth were surveyed on several occasions to determine the relationship between tar yield and symptom onset. There was little evidence of less symptom occurrence in the new smokers using low-tar cigarettes in comparison with those smoking higher-tar cigarettes. Moreover, symptoms were far more frequent in the low-tar smokers than in nonsmokers. In a randomized trial in the United Kingdom, lower tar cigarettes were not associated with either lower symptom frequency or a higher level of ventilatory function, which was assessed by measuring the peak expository flow rate (Withey et al. 1982a,b). The investigators monitored urinary nicotine metabolites and concluded that compensation led to comparable levels across the trial period.

Respiratory morbidity also has been investigated. Follow-ups of outpatient visits by enrollees in a Kaiser Permanente group over one year showed that there was a reduced risk for pneumonia and influenza, but not for other respiratory conditions, associated with the use of low-tar and low-nicotine products compared with the use of products higher in tar and nicotine (Perlet and Friedman 1985a). However, in comparison with nonsmokers, smokers using low-tar and low-nicotine cigarettes had an increased risk for pneumonia, influenza, and COPD.

The evidence does not suggest a relationship between tar yield and lung function level. For example, in the Whitehall Study there was no cross-sectional relationship between tar yield and the FEV_1 level (Higenbottam et al. 1980). In the Normative Aging Study, a longitudinal study of U.S. veterans, tar yields of the usual brands of cigarettes smoked were not associated with a decline of FEV_1 levels (Sparrow et al. 1983), and the Tucson Study found a weak association between lung function decline and higher tar yields (Krzyzanowski et al. 1991).

In general, cohort studies assessing cigarette type and yield with COPD risks show little evidence for an association. In the CPS-I study comparing "low-" or "medium-" tar and nicotine smokers with "high-" tar and nicotine smokers, mortality from emphysema was reduced somewhat, although not significantly (Table 4.18) (Lee and Garfinkel 1981).

Evidence Synthesis. Little new evidence is available, and it does not conflict with the conclusion of the 1984 Surgeon General's report (USDHHS 1984) that "reduction in cigarette tar content appears to reduce the risk of cough and mucus hypersecretion" (p. 12). Limited evidence published since that report suggests that cigarette type does not influence the rate of FEV_1 decline or COPD-related mortality.

Conclusions

1. The evidence is suggestive but not sufficient to infer a causal relationship between lower machine-measured cigarette tar and a lower risk for cough and mucus hypersecretion.

2. The evidence is inadequate to infer the presence or absence of a causal relationship between a lower cigarette tar content and reductions in forced expiratory volume in one second decline rates.

3. The evidence is inadequate to infer the presence or absence of a causal relationship between a lower cigarette tar content and reductions in chronic obstructive pulmonary disease-related mortality.

Implications. Although there are limited data on the relationship between cigarette type and the risk for chronic respiratory diseases, the strong benefits from smoking cessation combined with the availability of effective methods for controlling tobacco use suggest that little public health benefit will be gained by further research on the relationship between cigarette type and chronic respiratory diseases.

Diffuse Parenchymal Lung Diseases. Diffuse parenchymal lung diseases, also known as interstitial lung diseases, are a heterogeneous group of disorders associated with different types of inflammation primarily in the walls and airspaces of alveoli. Although there are more than 100 different diffuse parenchymal lung diseases, only small numbers of patients with the [illegible] are seen regularly by clinicians (Coultas et al. 1994), and the role of cigarette smoking has been investigated only for a few of these diseases.

Although the pathogenesis of these diseases is varied, conceptually they result from an inflammatory response in the lungs that follows the inhalation of a wide variety of particles (e.g., inorganic and organic). For some of the diseases (i.e., idiopathic pulmonary fibrosis [IPF] or sarcoidosis), emerging evidence suggests a causal role for a number of inhaled agents, but causality remains to be established. The role of cigarette smoking in the pathogenesis of diffuse parenchymal lung diseases, although not fully defined, is potentially complex and may involve altered clearance, deposition of particles, and modification of the inflammatory response. Evidence for a complex interaction between cigarette smoking and the pathogenesis of diffuse parenchymal lung diseases is based on observations that cigarette smoking is associated with an increased disease risk for some (e.g., IPF or pneumoconiosis), and a decreased risk for others (e.g., hypersensitivity pneumonitis or sarcoidosis). Available evidence suggests that modification of the inflammatory/immune response may be the mechanism for lowering the risks for hypersensitivity pneumonitis (Baron 1996) and sarcoidosis (Soliman and Twigg 1992; Baron 1996).

Idiopathic Pulmonary Fibrosis. *Epidemiologic Evidence.* Scant epidemiologic data are available on the occurrence of IPF (Coultas et al. 1994), but the available information suggests that IPF may be the most common diffuse parenchymal lung disease in the general population (Coultas et al. 1994). Until recently, etiologic investigations of this disorder had not been conducted. It is relatively uncommon, and without a lung biopsy misclassification of the diagnosis may result, making investigation of this disorder difficult. Although the term "idiopathic" means of unknown cause, during the past decade four case-control studies have been conducted to examine potential etiologic agents, including cigarette smoking (Scott et al. 1990; Iwai et al. 1994; Hubbard et al. 1996; Baumgartner et al. 1997). One case-control study of environmental exposures was conducted with 17 patients, but cigarette smoking was not examined (Mullen et al. 1998).

Overall, significant associations were found in three of the four studies. Scott and colleagues (1990) identified 40 cases of IPF seen by pulmonary physicians or tested at pulmonary function laboratories in Nottingham, England, and 108 age- and gender-matched controls were identified from patients registered with the index patient's general practitioner. In this case-control study, cigarette smoking was not significantly associated with IPF (OR = 1.11 [95 percent CI, 0.13–1.40]).

Cases of IPF seen between 1992 and 1994 at four teaching hospitals in the Trent Region, United Kingdom, were identified by Hubbard and colleagues (1996). Controls matched by age, gender, and community were identified from patients registered with the same general practitioner. Information on smoking and other exposures was obtained from 218 patients and 569 controls who returned a mailed questionnaire; 165 cases and 408 controls completed telephone interviews for verification. Having ever smoked was significantly associated with IPF (OR = 1.57 [95 percent CI, 1.01–2.43]).

Iwai and colleagues (1994) identified 86 patients with IPF evaluated by two research committees in Japan. Two controls for each patient were matched for age, gender, and residential area: a person selected from voters' lists and a hospital patient with a non-IPF respiratory disease. Compared with healthy controls, IPF patients were significantly more likely to smoke (OR = 2.94 [95 percent CI, 1.37–6.30]).

Baumgartner and colleagues (1997) conducted a multicenter case-control study in the United States that included 16 institutions in 15 states. A total of 249 patients had been diagnosed with IPF between 1989 and 1993; and 491 community controls matched for age, gender, and geographic location were identified using random-digit telephone dialing. Standardized telephone interviews were used to obtain risk factor information from cases and controls. Ever smoking

Table 4.18 Studies on the association between cigarette tar yields and chronic respiratory diseases

Study	Design/population	Variable studied
Dean et al. 1978	Sample of 12,736 men and women Aged 37–67 years Living in England, Scotland, and Wales [illegible]	Filter-tipped or unfiltered cigarettes
Hawthorne and Fox 1979	Prospective cohort study of 786 people identified as [illegible] attending chest clinics Followed from 1967 to 1972 in West Central Scotland	Filter-tipped or unfiltered cigarettes
Higenbottam et al. 1980	Prospective cohort study [illegible] Service Civil Servants Entry 1970 United Kingdom	Cigarette tar, nicotine, and tar yield
Lee and Garfinkel 1981	Prospective cohort study [illegible] volunteers aged 25–64 years 1 million men and women followed from 1959–1972	Cigarette type (high, medium, low tar and nicotine) Cigarettes/day
Schenker et al. 1982	Cross-sectional study Random sample of women in a standard metropolitan statistical area—Philadelphia	Cigarette tar and nicotine
Sparrow et al. 1983	Cohort study 1,305 men (25 [illegible] 59 [illegible] and 417 young smokers) participating in study from 1963–1974 in Boston, Massachusetts	Cigarette tar and nicotine
Krzyzanowski et al. 1991	Longitudinal study Random sample of adults Followed from 1972–1982	Cigarette tar and nicotine Type of cigarette
Perlet and Friedman 1985a	Prospective cohort study [illegible] 270 Kaiser Permanente members and 1,411 [illegible] between 1965–1970 Diagnosis of Followed from 1965–1980	Tar yield

[illegible] = Information not available.
[a]American Cancer Society Cancer Prevention Study I.
[b]RR = Relative risk.
[c]OR = Odds ratio.
[d]CI = Confidence interval.

Outcome	Findings
Respiratory symptoms	Morning coughs in men and women and shortness of breath in women were lower for filter-tipped cigarette smokers; estimates were adjusted for age, social class, number of cigarettes per day, inhalation, and occupation
Prevalence of respiratory symptoms	Among current cigarette smokers, filter-tipped cigarette smokers showed [illegible] than did plain-tipped cigarette smokers (OR = 0.68 [95% CI = 0.49–0.93] for chronic cough; OR = 0.72 [95% CI = 0.52–0.99] for chronic phlegm; OR = 0.72 [95% CI = 0.53–0.98] for chronic cough and phlegm; OR = 0.73 [95% CI = 0.53–1.00] for dyspnea; OR = 0.67 [95% CI = 0.49–0.91] for wheezing; and OR = 0.67 [95% CI = 0.49–0.92] for chronic bronchitis). Differences were adjusted for age
Lung function and respiratory symptoms	Low tar yields had no beneficial effect on lung function although [illegible] reduction in mucus hypersecretion and cough symptoms could have been due to less phlegm or other smoking-related factors
Lung physiology	Filter smokers showed less [illegible] and [illegible] RR = 0.78 for men and 0.69 for women [illegible] small differences between low- and high-tar yields
Several respiratory symptoms	High-tar smokers had a greater risk for [illegible] than did low-tar smokers (p < 0.05) and also had a greater risk for chronic phlegm [illegible] (p < 0.01). Chronic cough and COPD [illegible] chronic phlegm [illegible] were not associated with [illegible] of cigarette smoked per day
Lung function (by spirometry)	Daily [illegible] significantly [illegible] over the 2 years of [illegible] activity [illegible] daily [illegible] curve in [illegible] smokers. The [illegible] and the [illegible] of cigarettes
Chronic bronchitis	For smokers of [illegible] cigarettes, RR = 0.78 for men and 0.69 for women and for smokers of [illegible] RR = 1.0 for men and 0.9 for women
All respiratory diseases	RR = 0.77 (95% CI = 0.64–1.15) per 10 mg tar; no clear relationship between maternal smoking and risk of infant diseases of the respiratory system

Table 4.18 Continued

Study	Design/population	Variable studied
Rimpelä and Teperi 1984	Longitudinal study 2,266 men and w[illegible] from Finland, born between Ja[illegible] and July 31, 1966	Low yield
[illegible] 1991	P[illegible] S[illegible] fi[illegible] [illegible] between 1[illegible] and [illegible] current smokers and [illegible] than 20 cigarettes/d	Cigarette tar yield Low = [illegible] Middle = [illegible] High = [illegible]
Rimpelä et al. 1991	Prospective cohort study [illegible] in sample of [illegible] Finland Followed from 1[illegible]	[illegible] and [illegible] yields
Enright et al. 1992	F[illegible] C[illegible] smoked [illegible] 1 month before the [illegible] questionnaire F[illegible]	Filter-tipped vs. non-filtered cigarettes
Whitley et al. 1994a,b	[illegible] health authority districts in England; male mid[illegible] tar smokers aged 18–44 years; 7,029 smokers selected from 265,016 who were sent questionnaires; 843 controls; assigned 1 of 3 different types of cigarettes for 6 months Followed from 1985–1989	Middle[illegible] smokers (>12 mg/cigarette) were assigned to test low-tar/middle-nicotine cigarettes with 9.5 mg tar/1.16 mg [illegible] middle-tar/m[illegible] and [illegible] with 15[illegible] tar, 1.3[illegible] nicotine, or low-tar/low-nicotine cigarettes with [illegible]
Tverdy et al. 1995	4[illegible] [illegible] Project, [illegible] cigarettes [illegible] Study, [illegible] Family Services Study, [illegible] and UK Heart Disease Prevention Project (England and Wales)	Tar yield of cigarettes smoked [illegible] tar

Outcome	Findings
Respiratory symptoms (especially cough and phlegm)	Number of cigarettes/day was associated with morning cough, cough during day or night, and morning phlegm, on a significant or nearly significant level (p = 0.047–0.075), while no dependent variable was significantly related to phlegm during the day or night; tar yields played no role in the prediction of symptoms
Chronic coughs and chronic phlegm	Ratings [illegible] and elderly were greater for women who smoked higher-tar cigarettes than for those who smoked lower-tar cigarettes. Similar risks for women [illegible] cigarettes and for women who smoked [illegible] cigarettes (p = 0.75). RR was provided
Respiratory symptoms, pulmonary function	A [illegible] and [illegible] was [illegible] with morning and episodes of [illegible], there was no [illegible] with [illegible] phlegm, cough, or dyspnea [illegible] function. [illegible] with increasing [illegible]
Chronic obstructive pulmonary disease (COPD)-related mortality	Among [illegible] cigarette smokers, RR for men who smoked [illegible] cigarettes = 1.0 (p = [illegible]). [illegible] smoked [illegible] cigarettes = 1.1 (95% CI = 0.96–1.3)
Respiratory symptoms	There were no differences in respiratory symptoms after switching to different types of cigarettes. Urine nicotine metabolites analyses showed that smokers adjusted their smoking so that throughout the trial their nicotine inhalation differed little from their [illegible] nicotine intakes when they were smoking their usual cigarettes
Cell [illegible]	A [illegible] cigarette smokers was [illegible] in the [illegible] group (RR = 0.79, 95% CI, 0.47–1.48)

was significantly associated with IPF (OR = 1.6 [95 percent CI, 1.1–2.4]), but there was no dose-response relationship with pack-years of smoking. Moreover, there was no increased risk in current smokers (OR = 1.06 [95 percent CI, 0.6–1.8]). However, among former smokers there was an inverse trend in risk with time since cessation (OR = 3.5 [95 percent CI, 1.1–11.9] for cessation of less than 2.5 years, OR = 2.3 [95 percent CI, 1.3–4.2] for cessation of 2.5 to 10 years, OR = 1.9 [95 percent CI, 1.1–3.2] for cessation of 10 to 25 years, and OR = 1.3 [95 percent CI, 0.7–2.3] for cessation of 25 or more years).

Evidence Synthesis. Inflammation is thought to have a central role in the pathogenesis of IPF. Smoking, which increases lung inflammation, could plausibly increase the risk for IPF. Several studies show an association between ever smoking and IPF; however, the data are limited and further studies are needed.

Conclusion

1. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and idiopathic pulmonary fibrosis.

Implication. Further research will be needed to determine whether there is a causal relationship between active smoking and pulmonary fibrosis.

Conclusions

Acute Respiratory Illnesses

1. The evidence is sufficient to infer a causal relationship between smoking and acute respiratory illnesses, including pneumonia, in persons without underlying smoking-related chronic obstructive lung disease.
2. The evidence is suggestive but not sufficient to infer a causal relationship between smoking and acute respiratory infections among persons with preexisting chronic obstructive pulmonary disease.
3. In persons with asthma, the evidence is inadequate to infer the presence or absence of a causal relationship between smoking and acute asthma exacerbation.

Chronic Respiratory Diseases

4. The evidence is sufficient to infer a causal relationship between maternal smoking during pregnancy and a reduction of lung function in infants.
5. The evidence is suggestive but not sufficient to infer a causal relationship between maternal smoking during pregnancy and an increase in the frequency of lower respiratory tract illnesses during infancy.
6. The evidence is suggestive but not sufficient to infer a causal relationship between maternal smoking during pregnancy and an increased risk for impaired lung function in childhood and adulthood.
7. Active smoking causes injurious biologic processes (i.e., oxidative stress, inflammation, and a protease-antiprotease imbalance) that result in airway and alveolar injury. This injury, if sustained, ultimately leads to the development of chronic obstructive pulmonary disease.
8. The evidence is sufficient to infer a causal relationship between active smoking and impaired lung growth during childhood and adolescence.

9. The evidence is sufficient to infer a causal relationship between active smoking and the early onset of lung function decline during late adolescence and early adulthood.

10. The evidence is sufficient to infer a causal relationship between active smoking in adulthood and a premature onset of and an accelerated age-related decline in lung function.

11. The evidence is sufficient to infer a causal relationship between sustained cessation from smoking and a return of the rate of decline in pulmonary function to that of persons who had never smoked.

12. The evidence is sufficient to infer a causal relationship between active smoking and respiratory symptoms in children and adolescents, including coughing, phlegm, wheezing, and dyspnea.

13. The evidence is sufficient to infer a causal relationship between active smoking and asthma-related symptoms (i.e., wheezing) in childhood and adolescence.

14. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and physician-diagnosed asthma in childhood and adolescence.

15. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and a poorer prognosis for children and adolescents with asthma.

16. The evidence is sufficient to infer a causal relationship between active smoking and all major respiratory symptoms among adults, including coughing, phlegm, wheezing, and dyspnea.

17. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and asthma in adults.

18. The evidence is suggestive but not sufficient to infer a causal relationship between active smoking and increased nonspecific bronchial hyperresponsiveness.

19. The evidence is sufficient to infer a causal relationship between active smoking and poor asthma control.

20. The evidence is sufficient to infer a causal relationship between active smoking and chronic obstructive pulmonary disease morbidity and mortality.

21. The evidence is suggestive but not sufficient to infer a causal relationship between lower machine-measured cigarette tar and a lower risk for cough and mucus hypersecretion.

22. The evidence is inadequate to infer the presence or absence of a causal relationship between a lower cigarette tar content and reductions in forced expiratory volume in one second decline rates.

23. The evidence is inadequate to infer the presence or absence of a causal relationship between a lower cigarette tar content and reductions in chronic obstructive pulmonary disease-related mortality.

24. The evidence is inadequate to infer the presence or absence of a causal relationship between active smoking and idiopathic pulmonary fibrosis

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